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Dr. Sanjay Pandya

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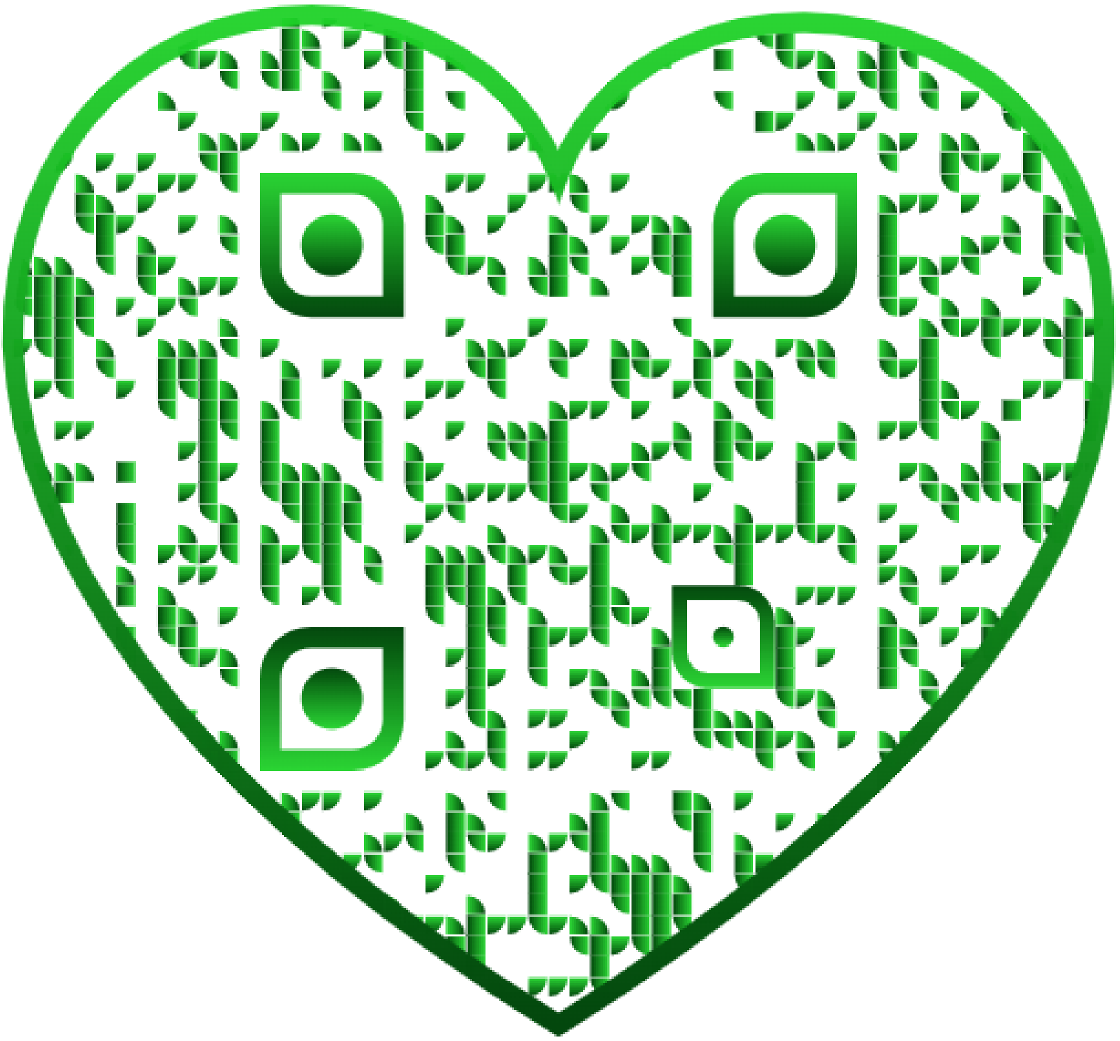

Practical Guidelines on Fluid Therapy

Dr. Sanjay Pandya, Consulting Nephrologist

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- Hemodynamic Monitoring
- Fluid Therapy in Medical & Surgical Disorders
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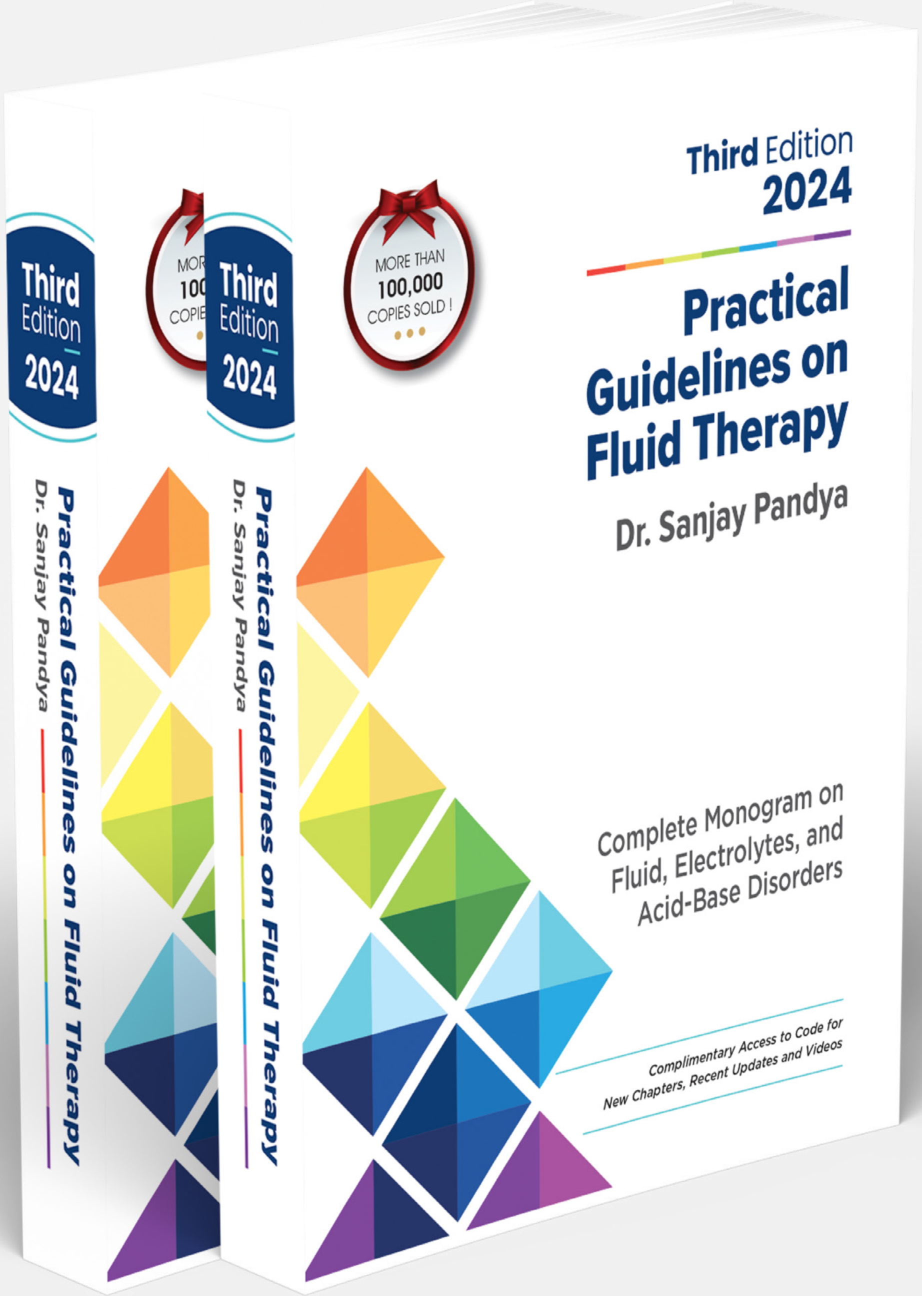
Chapter 1:

Basic Physiology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1 Basic Physiology

Total Body Water 3
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Fluid and Electrolytes Movement 4
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Water is the most abundant component of the body. Body fluid is essential for the life as it helps in transport of nutrients, electrolytes, gases, and wastes and also helps to maintain body temperature and cell shape. An understanding of the physiology of body fluids is essential to plan appropriate management of patients' fluid and electrolyte disorders. In this chapter, we will discuss the body's fluid compartments (i.e., their location, size, and composition), normal water balance, electrolytes, and their distribution, and finally, the units of measurement.

TOTAL BODY WATER

The total body water (TBW) content of a person varies mainly with body weight, but it also varies with age, sex, and fat content [1]. Total body water content is about 60% of body weight in a young adult male and about 50% in a young adult female [2]. Because the water content of adipose tissue is relatively low, an obese person will have proportionately less body water as compared to a lean person. The highest percentage of TBW is found in newborns (as high as 80%), which declines with age. The average total body water in different groups is shown in Table 1.1. The measurement of TBW can be performed via indicator dilution techniques using Deuterium oxide ($2H_2O$), tritium oxide ($3H_2O$), oxygen-18 labelled water, or more recently via bioelectrical impedance analysis [3].

Distribution of body fluid

Total body water is commonly divided into two volumes: the intracellular fluid (ICF) volume and the extracellular fluid (ECF) volume (Figure 1.1) [4].

Table 1.1 Average total body water as a percentage of body weight

Age	Adult male	Adult female	Elderly	Adult obese	Infant	Neonate
Total body water (% of body weight)	60%	50%	50%	50%	70%	80%

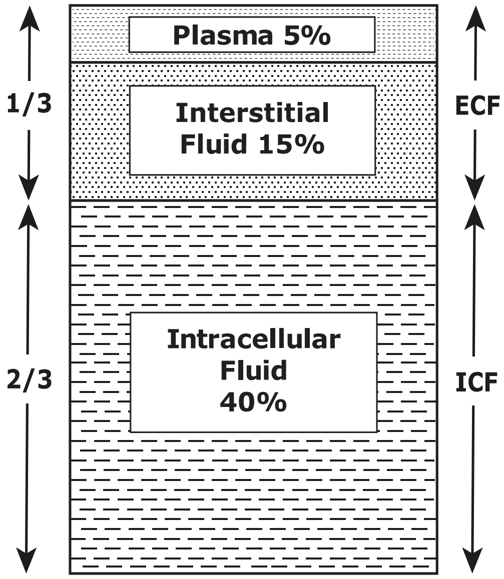

Figure 1.1 Body fluid compartments.

Intracellular fluid

ICF is defined as all the body water within cells. The ICF is normally two third of total body water and 40% of total body weight. Water balance regulates the ICF volume.

Extracellular fluid

ECF is defined as all body water outside the cells - within the tissue spaces (interstitial fluid), the blood vessels (intravascular fluid or plasma), and the lymphatic vessels (lymph). The ECF is normally one third of total body water and 20% of total body weight. As shown in Figure 1.1, ECF is subdivided into extravascular (interstitial) fluid (3/4th of ECF or 15% of total body weight) and plasma or intravascular volume (1/4th of ECF, 1/12 total body water or 5% of total body weight). There is another small compartment of ECF that is referred to as transcellular fluid. This compartment includes cerebrospinal fluid and fluid in the synovial, peritoneal, pericardial, and intraocular spaces. Sodium balance regulates the ECF volume.

For better understanding, the distribution of fluid volume in a 70 kg man is summarized in Table 1.2.

BODY FLUID AND ELECTROLYTES MOVEMENT

The movement of water and electrolytes between ICF and ECF compartments is regulated to stabilize their distribution and the composition of body fluids. The cell membranes that separate fluid compartments are selectively permeable. Water passes freely and readily through cell membranes in response to changes in solute concentration; therefore, the osmolalities in all compartments are equal. Two major determinants of water and electrolyte movements from one compartment to another are hydrostatic pressure and oncotic pressure [5]. Major water retaining solutes in ECF, ICF, and intravascular compartments are sodium, potassium, and plasma protein, respectively.

Unlike water, solutes cannot pass freely through cell membranes even though there is a significant difference in solute concentration between ICF and ECF. The movement of solutes occurs through active and passive transport mechanisms. Active transport by sodium-potassium pumps (Na^+-K^+-ATPase) is the major force maintaining the difference in

Table 1.2 Distribution of fluid volume in body compartments

Fluid type	Total	ICF	ECF	Interstitial	Plasma
% of body weight	60%	40%	20%	15%	5%
Volume for 70 kg weight	42.0 L	28.0 L	14.0 L	10.5 L	3.5 L

cation concentration between the ICF and ECF [2]. Sodium and potassium are compartmentalized into extracellular and intracellular spaces, respectively, by sodium-potassium pumps present in all cell membranes.

NORMAL WATER BALANCE

A healthy adult person consumes an average of 2000 ml of water per day. Fluid intake and output are balanced during steady-state conditions as summarized in Figure 1.2.

Daily water intake

Major sources of water intake are oral intake in the form of liquids (drinking water or beverages), water in food, and water synthesized in the body by oxidation. Thirst primarily regulates water intake. The loss of water increases osmotic pressure in the extracellular fluid, stimulating osmoreceptors in the brain's hypothalamus thirst center, which, in turn, triggers a sensation of thirst, prompting individuals to drink. Conversely, drinking and the resulting stomach distension inhibit the thirst mechanism.

Daily water loss

Routes of water loss are kidneys, feces, sweat (sensible perspiration), evaporation of water from the skin (insensible perspiration), and lungs during breathing. The kidney plays a major role in water balance. By regulating volume of urine, kidneys adjust water output from the body.

Oral or intravenous (IV) fluid intake and urine output are important measurable parameters of body fluid balance. While calculating the daily fluid requirement of the body, it is important to know and consider insensible fluid input and loss.

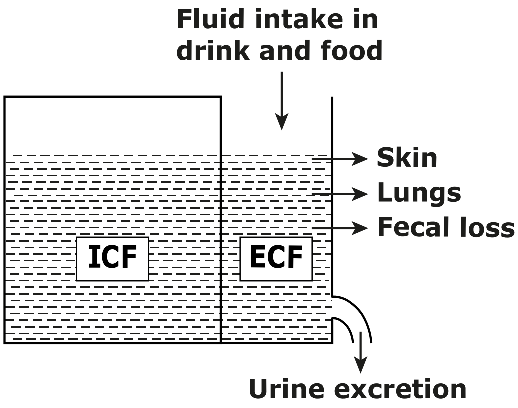

Figure 1.2 Daily water intake and loss in the body.

Insensible fluid input = 300 ml water due to oxidation.

Insensible fluid loss = 1000 ml (500 ml through the skin, 400 ml through the lung, and 100 ml through stool)

Normal Daily Insensible Fluid Loss =

Fluid Loss - Fluid Input = 1000 - 300 ml = 700 ml

Water loss is increased during exercise, excessive sweating, fever, burns, and surgery. This basic information is necessary to determine daily fluid requirements for patients receiving IV fluids. The daily fluid requirement for a normal person is calculated by adding together the amount of fluid lost in urine and insensible losses. In a normal person, the insensible daily loss is about 700 ml. So, daily fluid requirement = urine output + 700 ml.

DISTRIBUTION OF ELECTROLYTES

The normal electrolyte compositions of each fluid compartment differ markedly, as summarized in Tables 1.3 and 1.4. For example, the ECF compartment contains a high concentration of sodium, chloride, and bicarbonate but only a small quantity of potassium. In contrast,

Table 1.3 The electrolyte concentration of body fluids

Electrolytes	ECF (mEq/L)	ICF (mEq/L)
Sodium	142.00	10.00
Potassium	4.30	150.00
Chloride	104.00	2.00
Bicarbonate	24.00	6.00
Calcium	5.00	0.01
Magnesium	3.00	40.00
Phosphate and sulfate	8.00	15.00

Table 1.4 Major ions in ECF and ICF

	ECF	ICF
Major cation	Sodium	Potassium and magnesium
Major anion	Chloride and bicarbonate	Phosphate, sulfate and protein

the ICF compartment contains a high concentration of potassium, magnesium, phosphate, sulfate, and proteins. Furthermore, as sodium is confined chiefly to the ECF compartment, sodium-containing fluids are distributed throughout the ECF. As a result, sodium-containing fluids expand the volume of both the interstitial and intravascular spaces (the interstitial space expansion is approximately three times as much as the plasma).

UNITS OF MEASUREMENTS

It is important to understand the basic terminology used to measure the concentration and composition of body fluids and their interrelationship.

Ions: An ion is an atom or group of atoms with an electric charge. Ions are divided into anions and cations as shown in Figure 1.3.

Anion: When an ion has a negative electric charge, it is called an anion (i.e., Cl^-, HCO_3^-, phosphate).

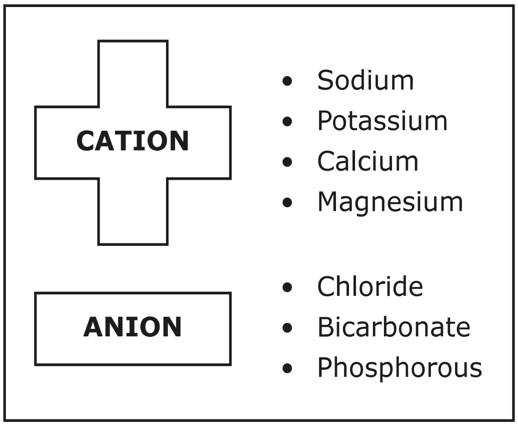

Figure 1.3 Major Cations and Anions.

Cation: When an ion has a positive electric charge, it is called a cation (i.e., Na^+, K^+, Mg^{2+}).

If cation and anion are confusing, here is a simple method to remember.

A**n**ion: **"n"** - negative charge

Ca**t**ion: **"t"** - + positive charge

Different ways by which solute concentrations can be measured are milligram per decilitre (mg/dL), milliequivalent per liter (mEq/L), or milliosmoles per liter or kg (mOsmol/L or mOsmol/kg).

Moles and millimoles

The unit millimole (mmol) is used in practice instead of mole (mol) for convenience as it is smaller and more practical to handle in medical and scientific settings.

$$6.022 \times 10^{23}$$

A mole represents a specific number of particles. One mole of any non-dissociable substance contains approximately 6.022×10^{23} particles. To clarify with an example, consider salt (NaCl). It contains an equal number of atoms: one sodium (Na^+) atom for every chloride (Cl^-) atom, even though they have different atomic weights, with 23 mg for Na^+ and 35.5 mg for Cl^-. If we compare one dozen mangoes to one dozen bananas, they represent the

Table 1.5 Atomic and molecular weights of important substances

Substances	Symbol or formula	Atomic or molecular weight
Calcium	Ca^{2+}	40.1
Carbon	C	12.0
Chloride ion	Cl^-	35.5
Hydrogen ion	H^+	1.0
Magnesium ion	Mg^{2+}	24.3
Oxygen	O	16.0
Phosphorus	P	31.0
Potassium ion	K^+	39.1
Sodium ion	Na^+	23.0
Ammonium	NH_4^+	18.0
Bicarbonate ion	HCO_3^-	61.0
Phosphate ion	PO_4^{3-}	95.0
Water	H_2O	18.0

same quantity of fruit, but their weights differ.

Mole: One mole (mol) of any substance is defined as the atomic or molecular weight of that substance in gm.

Similarly, one millimole (mmol) is equals to one-thousandth of a mole or the molecular (or atomic) weight in milligrams.

So to determine the amount of any substance in one mole, we need to know the atomic (molecular) weight of that substance (Table 1.5).

The atomic weight of Na^+ is 23. Thus, 23 mg of Na^+ represents 1 mmol. Therefore, 23 mg of Na^+ in 1 liter of water results in a Na^+ concentration of one mmol/L.

Equivalent and milliequivalent

The equivalent is a relative term; it refers to a mole of ionic charges.

Equivalent: The equivalent weight of an element is its atomic weight in gm multiplied by its valence.

For ions that carry a single charged mole equals an equivalent (i.e., Na^+, K^+, Cl^-, H^+). But if the ion carries a charge that is greater than one, numbers are no longer equal. So, for example, one mole of calcium ion (Ca^{2+}) equals two equivalents.

So, Equivalents = Moles × Valence

A comparison of the normal value of serum electrolytes concentration in mmol/L and mEq/L is shown in Table 1.6.

Molecules must be quantified in moles (e.g., a mole of glucose) because they carry no charge. However, in practice, they are usually measured in mg or gm because of their simplicity and convenience. The following formula can be used to convert mg/dL to mmol/L.

$$\text{mmol/L} = \frac{\text{mg/dL} \times 10}{\text{Atomic Weight}}$$

Ions can be quantified as either moles or equivalents.

Why are the terms "mmol" or "mEq" used instead of "moles" or "equivalents"?

In routine practice, we prefer using "mmol" (millimoles) or "mEq" (milliequivalents) to express concentrations rather

Table 1.6 Normal plasma electrolyte concentrations

Electrolyte	mEq/L	mmol/L
Cations		
Sodium	136 to 145	136 to 145
Potassium	3.5 to 5.0	3.5 to 5.0
Calcium total*	4.5 to 5.6	2.2 to 2.6
Ionized*	2.2 to 2.6	1.05 to 1.3
Magnesium*	1.4 to 1.7	0.70 to 0.85
Anions		
Chloride	96 to 106	96 to 106
Bicarbonate	22 to 26	22 to 26

*Value in mg/dL: The normal values for total calcium and ionized calcium are 8.5-10.5 mg/dL and 4.3-5.3 mg/dL, respectively. The normal value of magnesium is 1.7–2.1 mg/dL.

than "moles" or "equivalents" This preference arises from the extremely low concentrations of most molecules and ions in serum.

In day-to-day practice, we use a millimeter, which is 1/1000 of the meter. Similarly, "mmol" or "mEq" represents 1/1000 of a mole or equivalent. For example, consider the serum potassium value, which might be expressed as 0.004 moles or equivalents per liter. However, converting it to 4 mmol/L or mEq/L provides a more practical, straightforward, and convenient value for everyday use in clinical practice.

The relationship between mEq and mg

Formula to convert mg/dL to mEq/L: To convert from milligrams per deciliter (mg/dL) to milliequivalents per liter (mEq/L), you can use the following formula:

$$\text{mEq/L} = \frac{\text{mg/dL} \times 10 \times \text{Valence}}{\text{Mol. Weight}}$$

Example: If 1 gm of salt (NaCl) is added to 1 liter of water, what will be its concentration in mEq/L?

NaCl 1 gm/L = 1,000 mg/L = 100 mg/dL

Valence of NaCl = 1

Molecular weight = 58.5 (Na^+ mol. wt. 23 and Cl^- mol. wt. 35.5).

$$\text{mEq / L} = \frac{100 \times 10 \times 1}{58.5} = 17.1$$

1 gm NaCl/L = 17.1 mEq/L

So, 1 gm of NaCl contains 17.1 mEq sodium and 17.1 mEq chloride, or the Na^+ concentration of NaCl = 17.1 mEq/gm.

Formula to convert mEq/L to mg/dL: To convert mEq/L to mg/dL, you can use the following formula:

$$\text{mg/dL} = \frac{\text{mEq/L} \times \text{Mol. Weight}}{10 \times \text{Valence}}$$

Example: If 1 liter of NaCl solution contains 154 mEq of NaCl, what is the amount of NaCl in mg/dL?

NaCl mEq/L = 154

Molecular Weight = 58.5 (Na^+ mol. wt. 23 and Cl^- mol. wt. 35.5)

Valence = 1

$$\text{So, mg/dL} = \frac{154 \times 58.5}{10 \times 1} = 900.9$$

So, in a 1-liter solution of NaCl with 154 mEq of NaCl, there is 9009 mg/L of NaCl salt.

When 9009 is divided by 154, the result is 58.5.

Therefore, 100 ml of NaCl solution containing 1 mEq of NaCl has 58.5 mg of salt.

These values, derived from both equations (Na^+ concentration is 17.1 mEq/gm of NaCl, and 1 mEq contains 58.5 mg NaCl), are useful for the calculation and interchangeability of routinely used substances.

Conversion factors helpful in day-to-day practice are summarized in Table 1.7.

Examples of conversion

Find out K^+ concentration in mEq in 10 ml ampoule of 15% potassium chloride (KCl)

10 ml of 15% KCl = 1.5 gm KCl/ampoule

1 gm of KCl contains 13 mEq of K^+ (as per Table 1.7).

So, 1.5 gm KCl = 1.5 × 13 = 19.5 mEq of K^+.

Answer: 10 ml amp. of 15% KCl contains 19.5 mEq of potassium.

Find out Na^+ concentration in mEq in a 25 ml ampoule of 7.5% sodium bicarbonate ($NaHCO_3$)

25 ml of 7.5% $NaHCO_3$ = 1.86 gm of $NaHCO_3$ per ampoule

1 gm of $NaHCO_3$ contains 12 mEq of Na^+ (as per Table 1.7).

Table 1.7 Conversion between mEq and mg

Salt	mEq cation or anion/ gm of salt	mg of salt/ mEq
Sodium chloride	17	58
Potassium chloride	13	75
Sodium bicarbonate	12	84
Calcium gluconate	4	224
Calcium chloride	14	73
Magnesium sulfate	8	123

So, 1.86 gm of $NaHCO_3$ = 1.86 × 12 = 22.3 mEq of Na^+.

Answer: A 25 ml ampoule of 7.5% $NaHCO_3$ contains 22.3 mEq of Na^+.

Osmotic pressure and osmolality

Osmotic pressure

Osmotic pressure determines the distribution of water among the different fluid compartments, particularly between the ECF and ICF.

The osmotic pressure generated by a solution is proportional to the number of particles per unit volume of solvent, not to the type, valence, or weight of the particles. To generate osmotic pressure, the solute must be unable to cross the cell membrane.

Osmole (Osm)

It is the unit of measurement of osmotic pressure. One osmole is defined as 1 gm molecular weight (1 mol) of any nondissociable substance (such as glucose) and contains 6.022×10^{23} particles.

Milliosmoles (mOsm)

mOsm is 1/1000 of an osmole. So in relatively diluted fluids in the body, the osmotic pressure is measured in milliosmole per kg of water (mOsm/kg).

An osmole (or mOsm) of a substance, such as glucose which does not dissociate into ions, is the same as a mole (or mmol). However, a mole of salts such as sodium chloride, which dissociates almost completely into sodium and chloride ions, equals 2 osmoles.

Osmolality and osmolarity

These laboratory values reflect the relationship between solute and solvent.

Osmolality

The osmolality of a solution is determined by the amount of solute dissolved in a solvent (i.e., water) measured in weight (kg).

If a solute is dissolved in 1 kg of water (solvent), the concentration of the solution is called osmolality and is expressed as mOsm/kg of the water solvent.

When osmolality is high, the solution is more concentrated, and when osmolality is low solution is diluted.

Osmolarity

The osmolarity of a solution is determined by the amount of solute dissolved in a solvent (i.e., water) measured in volume (liter).

If a solute is dissolved in 1 litre of water (solvent), the concentration of solution is called osmolarity and is expressed as mOsm/L.

Remember

When the solvent is measured in lite**r** - **"r"** - Osmolarity

and when the solvent is measured in Ki**l**ogram - **"l"** - Osmolality

As the temperature can affect the volume of solvent and solute in the solution, it can affect the value of the solution's osmolarity.

So osmolality (mOsm/kg), determined by the solvent's weight, is more accurate than osmolarity. However, the difference between these two values is negligible, and osmolarity is easier to measure, so it is used more commonly.

The osmolality of any solution is measured by measurement of its freezing point.

Plasma osmolality

Plasma osmolality is primarily determined largely by sodium salts, with a lesser contribution from ions, glucose, and urea. Normal plasma osmolality is 285 (275–295) mOsm/kg.

$$\text{Plasma Osmolality} = 2 \times \text{Na}^+ + \frac{\text{Glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}$$

Effective osmolality

Those solutes determine the effective osmolality of the extracellular fluid (ECF), which does not freely permeate the cell membrane and act to hold water within the ECF.

Lipid-soluble solutes like urea, which can pass through cell membranes, do not affect the difference in osmotic pressure between the ECF and ICF. So, urea which contributes to the calculation of plasma osmolality does not contribute to effective osmolality. Therefore, total osmolality and effective osmolality are different.

$$\text{Effective Osmolality (mOsm / kg)} = 2 \times \text{Na}^+ \text{ (mEq/L)} + \frac{\text{Glucose (mg/dL)}}{18}$$

Under normal circumstances, glucose accounts for only 5 mOsm/kg in effective osmolality. So normally, plasma sodium concentration is the determinant and reflector of the plasma osmolality.

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Fluid
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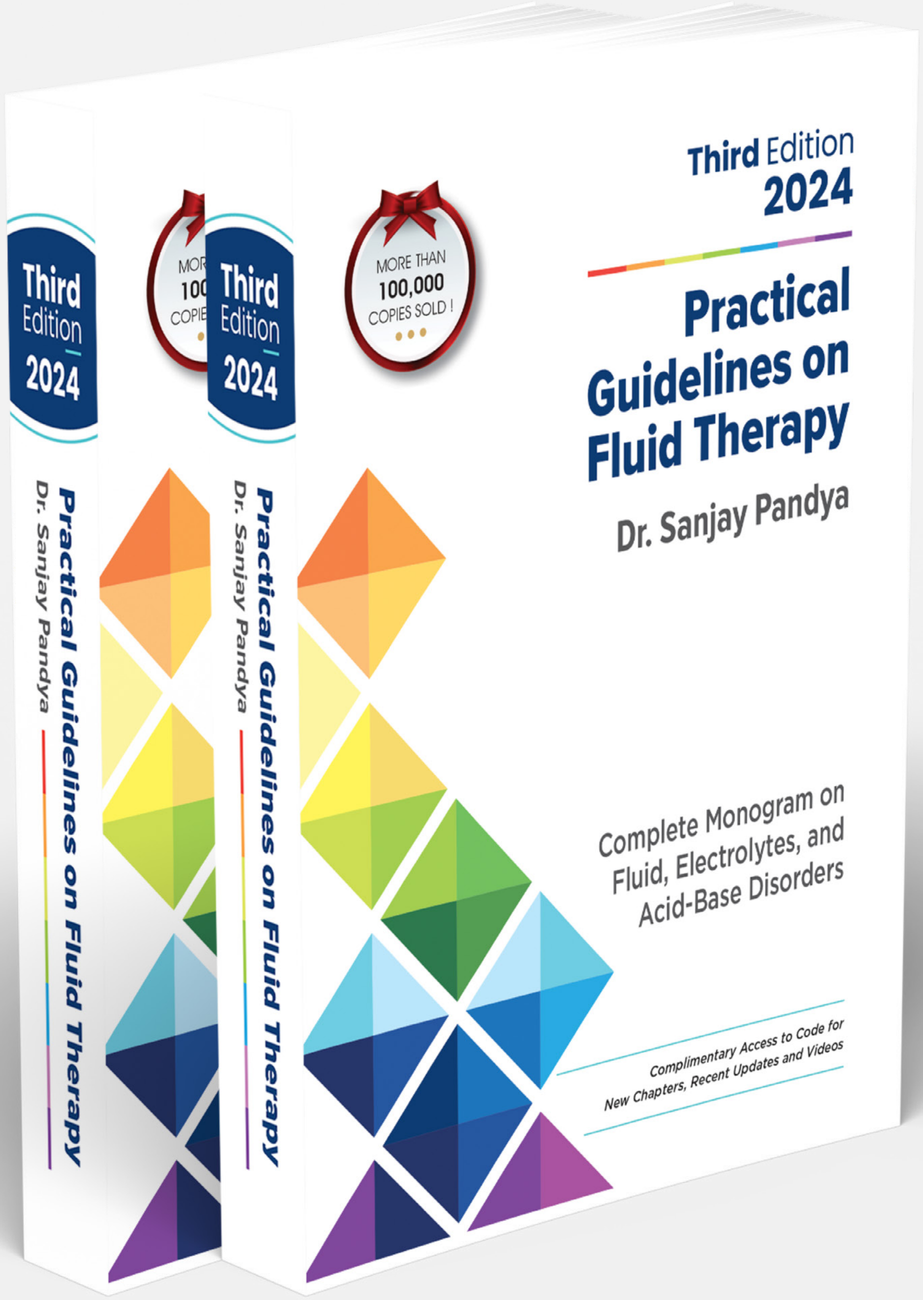
Chapter 2:

Overview of Intravenous Fluids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2

Overview of Intravenous Fluids

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Calculating Drop Rates for Fluid Infusion 20

A significant number of hospitalized patients across various medical specialties require intravenous (IV) fluid therapy. Understanding the fundamental principles is crucial for the safe and effective administration of IV fluids [1]. Inadequate fluid management can exacerbate patient outcomes and prolong hospital stays [2].

To prescribe appropriate fluid therapy, it is essential to consider the following:

- The underlying cause of fluid deficit and the type of electrolyte imbalance present.
- Coexisting medical conditions (e.g., diabetes, hypertension, ischemic heart disease, renal or hepatic disorders).
- Clinical status, including factors like age, hydration level, vital signs, urine output, etc.

To ensure rational and adequate fluid therapy, it is imperative to address the following questions:

- When is IV fluid administration appropriate, and when should it be avoided?
- Which type of fluid should be infused, and why?
- How much fluid should be administered, and what is the calculation method?
- At what rate should IV fluid be infused, and how is the drop rate calculated?
- What are the contraindications for various types of IV fluids, and what are the reasons behind them?
- How do you select IV fluids to correct electrolyte imbalances?
- When and how should specific fluids be used?

Following a comprehensive evaluation, the necessary fluid therapy is planned and prescribed.

BASIC PRINCIPLES OF FLUID THERAPY

As a principle, the oral route is always preferred over the IV route. But IV fluid

Table 2.1 Composition of common IV solutions

	Dext.*	Calories	Na^+	K^+	Cl^-	Acet.	Lact.	NH_4	Ca^{2+}	Mg^{2+}	HPO_4	Gluc.	Citr.	Osm.	SID
	gm/L	kcals/L	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mEq/L	mOsm/L	mEq/L
5% dextrose	50	170	-	-	-	-	-	-	-	-	-	-	-	252	0
10% dextrose	100	340	-	-	-	-	-	-	-	-	-	-	-	505	0
0.45% saline	-	-	77	-	77	-	-	-	-	-	-	-	-	154	0
D5W, 0.45% saline	50	170	77	-	77	-	-	-	-	-	-	-	-	406	0
Normal (0.9%) saline	-	-	154	-	154	-	-	-	-	-	-	-	-	308	0
Dextrose saline	50	170	154	-	154	-	-	-	-	-	-	-	-	560	0
Ringer’s lactate	-	-	130	4.0	109	-	28	-	3.0	-	-	-	-	273	28
Ringer’s acetate	-	-	130	5.0	112	27	-	-	3.0	2.0	-	-	-	276	27
PlasmaLyte	-	-	140	5.0	98	27	-	-	-	3.0	-	23	-	295	50
Sterofundin	-	-	145	4.0	127	24	-	-	5.0	2.0	-	-	-	309	29
Isolyte-G	50	170	63	17	150	-	-	70	-	-	-	-	-	578	NA
Isolyte-M	50	170	37	35	37	20	-	-	-	-	15	-	-	415	NA
Isolyte-P	50	170	25	20	24	23	-	-	-	3.0	3.0	-	-	348	NA
Isolyte-E	50	170	140	10	103	47	-	-	5.0	3.0	-	-	8.0	595	57
Isolyte-S	-	-	141	5.0	98	27	-	-	5.0	3.0	1.0	23	-	295	NA

Dext.: Dextrose	Cl^-: Chloride	NH_4: Ammonium	HPO4: Phosphate	SID: Strong ion difference
Na^+: Sodium	Acet.: Acetate	Ca^{2+}: Calcium	Citr.: Citrate	Gluc.: Gluconate
K^+: Potassium	Lact.: Lactate	Mg^{2+}: Magnesium	Osm.: Osmolality	

*Dextrose concentration is in gms/L

therapy has great importance and is life-saving in various clinical problems.

The basic principles of IV fluid therapy are summarized.

Indications

Fluid therapy is widely used for resuscitation, for proving the maintenance need of fluids, replacing and restoring fluids and electrolytes deficits, as a drug carrier, and for nutrition [3]. The most common and important indications for fluid administration includes:

1. For resuscitation in moderate to severe dehydration and shock, where urgent and rapid fluid replacement is needed.
2. To provide maintenance need in conditions when oral intake is not possible or is insufficient (i.e., coma, anesthesia, surgery).
3. To restore or replace fluid losses (e.g., severe vomiting, diarrhea, fever, burns, etc.), third space fluid loss (e.g., sepsis, burns, ascites, pancreatitis, or ileus), or blood losses (e.g., trauma or surgery).
4. To correct electrolytes and acid-base disorders.
5. To correct severe hypoglycemia, where IV 25% dextrose is life-saving.
6. As a vehicle for various IV medications (e.g., antibiotics, chemotherapeutic agents, insulin, vasopressor agents, etc.).
7. To provide parenteral nutrition.
8. Treatment of critical problems: Shock, anaphylaxis, severe asthma, cardiac arrest, forced diuresis in drug overdose, poisoning, etc.
9. To monitor hemodynamic functions and administer diagnostic reagents.

Contraindications

1. IV fluid should be avoided if the patient can take oral fluid.
2. Preferable to avoid IV fluid in a patient with congestive heart failure or volume overload.

Advantages

1. A perfect, controlled, and predictable way of fluid administration.
2. Immediate response is achieved through direct infusion into the intravascular compartment.
3. Rapid correction of life-threatening fluid and electrolyte disturbances.

Disadvantages

1. More expensive and needs strict asepsis.
2. Feasible only in hospitalized patients under supervision.
3. Improper selection of the type of fluid used can lead to serious problems.
4. The inappropriate volume and rate of infusion of fluid can be life-threatening.
5. The incorrect administration technique can lead to complications.

Complications

1. **Local:** Haematoma, infiltration, and infusion phlebitis.
2. **Systemic:** Circulation overload with rapid or large volume infusion, especially in patients with cardiac problems. Rigors, air embolism, and septicemia.
3. **Others:** Fluid contamination, fungus in IV fluids, mixing of incompatible drugs, an incorrect infusion technique, IV set or IV catheter-related problems, and human error-related problems.

OVERVIEW OF COMPOSITION OF IV FLUIDS

It is important to know the compositions of different commercially available IV fluids (Table 2.1) when making an appropriate choice for specific situations.

Bird's eye view of IV fluid characteristics

Before discussing the detailed composition and pharmacology of IV fluids, let's first assess and clarify the fundamental concept of IV fluids.

The physiological IV fluids

Balanced crystalloids such as Ringer's lactate (RL), PlasmaLyte, and Sterofundin are physiological IV fluids. Among these, RL is the most commonly used balanced crystalloid, with its electrolyte contents similar to the composition of the extracellular fluid (ECF) (Na^+-130 mEq/L, K^+-4 mEq/L, Cl^-109 mEq/L, lactate (bicarbonate) 28 mEq/L, and Ca^{2+}-3 mEq/L).

Daily normal maintenance requirement and preventing starvation ketosis in adults

Understanding the daily normal maintenance requirements for water, sodium, potassium, and the amount of dextrose needed to prevent starvation ketosis in adults is essential. These details are summarized in Table 2.2 [4].

Sodium content in various IV fluids

Understanding the sodium content in commonly used IV fluids is crucial. Among these fluids, normal saline (NS) and dextrose saline (D5NS) contain the maximum amount of sodium, with 154 mEq/L or 9 gm of NaCl per liter. (Note: 1 gm of NaCl contains 17.1 mEq Na^+). For detailed information on the sodium content of various IV fluids, refer to Table 2.3.

Chloride content in various IV fluids

Determining the chloride content in commonly used IV fluids is important. Among these fluids, normal saline, D5NS, and Isolyte-G all contain the maximum chloride concentration at 154 mEq/L.

Potassium content in various IV fluids

Understanding the potassium content in different IV fluids is essential. The potassium content of various IV fluids is summarized in Table 2.4.

It's crucial to note that Isolyte-M has the highest potassium content, with 35 mEq/L. In contrast, balanced crystalloids such as RL, PlasmaLyte, and Sterofundin contain only 4–5 mEq/L of potassium.

Table 2.2 Maintenance requirement of water, sodium, potassium and dextrose

	Water	Sodium	Potassium	Dextrose
Normal requirement	25–30 mL/kg/day	1 mEq/kg/day	1 mEq/kg/day	100 gm/day to prevent starvation ketosis

Table 2.3 Sodium concentration of IV fluids

IV Solutions	NS D5NS	Sterofundin	Plasma-Lyte	RL	0.45% NaCl	Isolyte-G	Isolyte-M	Isolyte-P	3% NaCl
Sodium mEq/L	154.0	145.0	140.0	130.0	77.0	63.0	37.0	25.0	513.0

Table 2.4 Potassium concentration of IV fluids

IV solutions	Isolyte-M	Isolyte-P	Isolyte-G	PlasmaLyte	RL and sterofundin	Inj. potassium chloride 15%
Potassium (mEq/L)	35.0	20.0	17.0	5.0	4.0	20 mEq/10 ml

Magnesium content in various IV fluids

IV fluids that contain magnesium include Ringer's acetate and Sterofundin, which contain 2 mEq/L, and solutions like PlasmaLyte, Isolyte-P, Isolyte-E, and Isolyte-S, which contain 3 mEq/L.

Calcium content in various IV fluids

IV fluids that contain calcium include Ringer's lactate and Ringer's acetate, which contain 2 mEq/L, while Sterofundin, Isolyte-E, and Isolyte-S contain 5 mEq/L.

Phosphate content in various IV fluids

Phosphate-containing IV fluids include Isolyte-M, which contains 15 mEq/L, and Isolyte-P, which contains 3 mEq/L.

Correction of acidosis with IV fluids

Understanding which IV fluids can directly correct acidosis and its mechanism is essential. Some IV fluids contain bicarbonate precursors, such as lactate and acetate [5]. Ringer's lactate, for example, contains 28 mEq/L of lactate, which is converted into bicarbonate in the liver, effectively correcting metabolic acidosis. Additionally, fluids like PlasmaLyte, Sterofundin, Isolyte-P, and Isolyte-M contain acetate (PlasmaLyte = 27 mEq/L, Sterofundin = 24, Isolyte-P = 23, and Isolyte-M = 20 mEq/L). Acetate also undergoes conversion into bicarbonate, both in the liver and peripheral tissues, aiding in the correction of metabolic acidosis.

Correction of metabolic alkalosis with IV fluids

Understanding which IV fluids can directly correct metabolic alkalosis is important. Isolyte-G stands out as the only IV fluid capable of directly addressing metabolic alkalosis. This effect is achieved through the presence of ammonium chloride (NH_4Cl = 70 mEq/L) in Isolyte-G, which undergoes conversion into H^+ ions and urea in the liver. The addition of H^+ ions effectively corrects the alkalosis.

Cautious use of IV fluids in renal failure

It is essential to exercise caution when using certain IV fluids in patients with renal failure. IV fluids with high sodium content, such as normal saline, dextrose saline (154 mEq/L sodium or 9 gm of salt per liter), and Ringer's lactate (130 mEq/L or approximately 7 gm of salt per liter), are administered with care due to their potential risk of fluid overload.

Furthermore, IV fluids containing a high potassium content, such as Isolyte-M, Isolyte-P, and Isolyte-G, should also be used cautiously in renal failure patients because of the potential risk of hyperkalemia.

Additionally, it's important to note that ammonium chloride in Isolyte-G undergoes conversion into hydrogen ions and urea, which can potentially exacerbate uremic acidosis, further emphasizing the need for caution when administering this fluid to individuals with renal issues.

Glucose-free IV fluids

It's important to note that normal saline, Ringer’s lactate, PlasmaLyte, and Sterofundin do not contain glucose. Therefore, they can be administered without the risk of worsening hyperglycemia.

Sodium and chloride free IV fluids

Among commonly used IV fluids, 5%,

10%, and 20%-dextrose are the only fluids that do not contain sodium and chloride. On the other hand, fluids like Isolyte-M and Isolyte-P have relatively low sodium and chloride content.

Potassium-free IV fluids

IV fluids such as normal saline, dextrose saline (D5NS), and 5%, 10%, and 20%-dextrose do not contain potassium.

CLASSIFICATION OF FLUIDS

The solutions used in intravenous fluid therapy are classified into the following based on the composition of fluids, osmolality, presence of buffers (in balanced solutions), and electrolytes.

A. Classification based on composition

The solutions used in intravenous fluid therapy are classified into three groups based on composition:

1. Crystalloids
2. Colloids
3. Whole blood and blood products

1. Crystalloids

Crystalloids are solutions in sterile water which contain varying concentrations of electrolytes and dextrose.

2. Colloids

Colloids are a solution containing water, electrolytes, and plasma-derived protein or semi-synthetic starch molecules that remain uniformly distributed and do not readily cross semi-permeable membranes. Colloids are frequently called volume expanders or plasma expanders. Commonly used Colloids include albumin, hydroxyethyl starch, gelatine, and dextran.

B. Classification of crystalloids based on osmolality

Crystalloids are classified into three categories according to their osmolality (Table 2.5).

1. Isotonic crystalloids

A crystalloid solution that has the same concentration of electrolytes as the body plasma. Isotonic fluids have an osmolality of 270–310 mOsm/L. When an isotonic crystalloid is administered, the infused isotonic solution remains within the extracellular fluid compartment (distributed between the intravascular and interstitial spaces), and therefore, isotonic IV fluids expand the intravascular compartment more effectively than hypotonic IV fluids [3]. Isotonic fluids don’t move into cells, and thus cells neither swell nor shrink with the isotonic fluid infusion.

Examples of isotonic solutions with their respective osmolarity values include 0.9% sodium chloride (308 mOsm/L), Ringer's lactate (273 mOsm/L), Ringer's acetate (276 mOsm/L), PlasmaLyte (295 mOsm/L), and Sterofundin (309 mOsm/L).

2. Hypotonic crystalloids

Crystalloid solutions with a lower concentration of electrolytes than body plasma are hypotonic fluids. Hypotonic fluids have an osmolality of less than 270 mOsm/L (lower than serum osmolarity). When hypotonic crystalloid is administered, the fluid will quickly move from the intravascular space into the cells and interstitial spaces. These solutions will hydrate cells causing them to swell. Examples of hypotonic solutions are 0.45% sodium chloride, 0.33% sodium chloride, 5% dextrose, 10% dextrose and D5W + 0.45% NaCl.

Table 2.5 Classification of crystalloid solutions according to osmolality

Characteristics	Isotonic solutions		Hypotonic solutions		Hypertonic solutions	
Osmolality (mOsm/L)	270–310		Lesser than 270		Greater than 310	
Distribution and effect on fluid compartment	Remains within ECF and expands ECF compartment		Fluid quickly moves from the intravascular space into the cells		Pull water from the cells into the intravascular space	
Effect on cell size	No effect		Swollen		Shrink	
Examples	Solutions	Osmolality mOsm/L	Solutions	Osmolality mOsm/L	Solutions	Osmolality mOsm/L
Normal serum osmolality is 275–295 mOsm/kg	0.9% NaCl	308	0.45% NaCl	154	3% NaCl	1026
	Ringer's lactate	273	0.33% NaCl	103	D5W + 0.9% NaCl	560
	PlasmaLyte	290	-	-	-	-

The 5% dextrose solution, with an osmolality of 252 mOsm/L, is often considered near isotonic in the bag. However, once it enters the body, dextrose is rapidly metabolized, leaving behind pure water, which becomes hypotonic. Similarly, the 10% dextrose solution has an osmolality of 505 mOsm/L in vitro, but it becomes pure hypotonic water in vivo with zero osmolality.

Additionally, D5W + 0.45% NaCl is hypertonic in the bag, with an osmolality of 406 mOsm/L. Nevertheless, once administered in the body, dextrose is rapidly metabolized, leaving behind a solution containing only 0.45% NaCl, which offers an osmolality of just 154 mOsm/L, making it hypotonic. Therefore, when using the above-mentioned IV fluids, selection should be based on the expected in vivo osmolality rather than what is mentioned on the package label [6].

Use hypotonic fluid with caution. As hypotonic fluid quickly moves from the intravascular space into the cells, vascular bed volume decrease. Depletion of intravascular fluid volume can exacerbate preexisting hypovolemia and hypotension and carries the risk of cardiovascular collapse. As hypotonic fluid can cause or exacerbate cerebral edema, avoid it in patients who are at risk for increased intracranial pressure (stroke, head injury, or neurosurgery) [7].

3. Hypertonic crystalloids

Crystalloid solutions with a higher concentration of electrolytes than body plasma are considered hypertonic fluids, which have an osmolarity of more than 310 mOsm/L or higher. Among the most widely used hypertonic solutions are 3% sodium chloride and 5% dextrose in 0.9% saline.

When hypertonic crystalloid solutions are administered, they draw water from the cells into the intravascular space, causing the cells to shrink and increasing extracellular fluid volume. This characteristic makes 3% sodium chloride a mainstay of treatment for cerebral edema since it can shrink brain cell size without the risk of hypotension, due to its ability to expand the extracellular fluid volume.

5% dextrose in 0.9% saline is not used for the treatment of cerebral edema because, in vivo, after the metabolism of glucose, it becomes similar to normal saline, which is an isotonic fluid.

As hypertonic fluid increases extracellular fluid volume, it carries the risk of volume overload and pulmonary edema and, therefore, should be avoided in cardiac or renal patients with circulatory overload. As hypertonic fluid causes cell shrinkage, it should be avoided in conditions causing cellular dehydration.

C. Classification of crystalloids based on buffers and electrolytes

For proper selection of crystalloids, we need to know the composition, pharmacological basis, important indications, and contraindications of commonly used IV fluids. The following crystalloids are discussed here.

1. Dextrose and sodium chloride solutions

5% dextrose, normal saline, dextrose saline, half normal saline, and half normal saline with dextrose.

2. Balanced crystalloids

Ringer’s lactate, Ringer's acetate, PlasmaLyte, and Sterofundin.

3. Multiple electrolyte solutions

Isolyte-G, Isolyte-M, Isolyte-P, Isolyte-E and Isolyte-S.

METHODS FOR CALCULATING DROP RATES PER MINUTE FOR FLUID INFUSION

In most non-ICU setups, electronic pump systems are unavailable, and fluids are administered via either macrodrip tubing (conventional, routine IV sets) or microdrip tubings. In such scenarios, manual calculation is necessary to determine the volume of fluid administered within a given time frame at required rates of drops per minute. It's essential to verify the drop factor of the administration set, which is used to ensure accurate fluid delivery during infusion therapy. Calculations differ based on either macrodrip tubing, which delivers larger-sized drops, or microdrip tubing, which provides smaller-sized drops.

A. Calculation for macro drip tubing

Commercially available macro drip tubing delivers larger drops, with the specific drop factor varying depending on the manufacturer's location and practices worldwide. Each milliliter of fluid administered through macro drip tubing typically delivers 10, 15, or 20 drops of fluid, known as the administration set drop factor (drops/mL).

- A drop factor of 10 drops/mL means that 10 drops of fluid will equal one milliliter.
- A drop factor of 15 drops/mL means that 15 drops of fluid will equal one milliliter.
- A drop factor of 20 drops/mL means that 20 drops of fluid will equal one milliliter.

The method used to calculate macro drop rates per minute for fluid infusion:

Step 1: First, convert the total volume of fluid to be delivered over a given time period into volume in an hour.

Volume/hour = Total Volume of Fluid (ml) / Duration of Time (hour)

Step 2: Convert the volume of fluid to be delivered in an hour into the volume given in a minute.

Volume/min = Total Volume of Fluid (ml) / 60

Step 3: Convert the volume of fluid to be delivered in a minute into the number of macro drops to be delivered in a minute.

Macro Drops/min = Total Volume of Fluid (ml) × Drop Factor of Macro Drip Tubing

Example: A patient needs 600 mL of intravenous fluids over 5 hours using macrodrip tubing with a drop factor of 15 drops/mL. Calculate the macro drop rates per minute.

- Volume/hour = 600 ml/5 hours = 120 ml/hour
- Volume/min = 120 ml/60 min = 2 ml/min
- Macro drops/min = 2 ml × 15 = 30 macro drop rates per min

Simple formulas for macro drip tubing with a drop factor of 15 drops/mL: A simple, practical, and user-friendly method for roughly calculating drop rates when macro drip tubing with a drop factor of 15 drops/mL is used to infuse IV fluids is summarized below.

Rule of ten: Multiply the volume of IV fluid to be delivered in liters over 24 hours by ten to obtain the drop rate per minute.

IV Fluid in Liters/24 hours × 10 =
Macro Drop Rate/min

- 2.0 liters in 24 hours = 2.0 × 10 = 20 macro drops/min
- 3.5 liters in 24 hours = 3.5 × 10 = 35 macro drops/min
- Calculation for 1 liter in 8 hours = 3.0 liters in 24 hours = 3.0 × 10 = 30 macro drops/min
- Calculation for 1 liter in 6 hours = 4.0 liters in 24 hours = 4.0 × 10 = 40 macro drops/min

Rule of four: Divide the volume of fluid (in ml) to be infused in one hour by four to obtain the macro drop rate per minute.

Volume in ml/hour ÷ 4 =
Macro drop rate/min

- 60 ml/hour = 60 ÷ 4 = 15 drops/min
- 200 ml/hour = 200 ÷ 4 = 50 drops/min

B. Calculation for micro drip tubing

Commercially available micro drip tubing delivers small-sized drops, with typically 1 mL providing 60 micro drops.

The formula to calculate micro drop rates per minute is simple.

Volume in ml/hour =
Number of Micro drops/min

- 30 ml/hour = 30 Micro drops/min
- 45 ml/hour = 45 Micro drops/min

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Chapter 3:

Dextrose and Sodium Chloride Solutions

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Crystalloids are solutions in sterile water which contain varying concentrations of electrolytes and dextrose. Dextrose and sodium chloride containing crystalloid solutions are discussed (Summarized in Table 3.1).

5% DEXTROSE (D5W)

Composition

One liter of fluid contains:

Dextrose	50 gm
Osmolality	252 mOsm/L
Caloric value	170 kcal/L
pH	4.3 (3.2 to 6.5)

Each 100 ml contains: Hydrous Dextrose USP 5 gm

Pharmacological basis

5% dextrose (usually abbreviated as D5W) provides free water with glucose without electrolytes. D5W is selected when there is a need for water but not electrolytes.

When a patient requires pure water, we administer intravenous 5% dextrose. Intravenous administration of free water is avoided due to its potential to cause hemolysis of red blood cells. However, the addition of dextrose renders the fluid near isotonic (252 mOsm/L) and does not result in hemolysis within the body.

5% dextrose packed in the bag is an isotonic solution, but once infused becomes a hypotonic solution in the body as dextrose is consumed rapidly, and the remaining plain water is hypotonic [1].

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Chapter 4:
Balanced and Multi-electrolyte Solutions

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4

Balanced and Multi-electrolyte Solutions

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Balanced and a few multi-electrolyte solutions are discussed in this chapter. Crystalloids with a composition closely resembling extracellular fluid have been termed 'balanced' or 'physiological' solutions [1, 2]. Balanced crystalloids are also distributed throughout the extracellular fluid (ECF) and are, therefore, of similar efficacy to normal saline (0.9% NaCl) in terms of plasma volume expansion.

Balanced crystalloids contain somewhat less sodium and significantly less chloride and therefore have advantages over normal saline solution when used for resuscitation or routine maintenance. Due to the instability of bicarbonate-containing solutions in plastic containers, alternative buffers such as lactate, acetate, gluconate, and malate are used to provide bicarbonate in balanced crystalloids [3]. Ringer's lactate is the most widely used balanced crystalloid.

RINGER'S LACTATE (RL)

Ringer's lactate solution is also known as Hartmann's solution, sodium lactate solution, or lactated Ringer's solution (LR).

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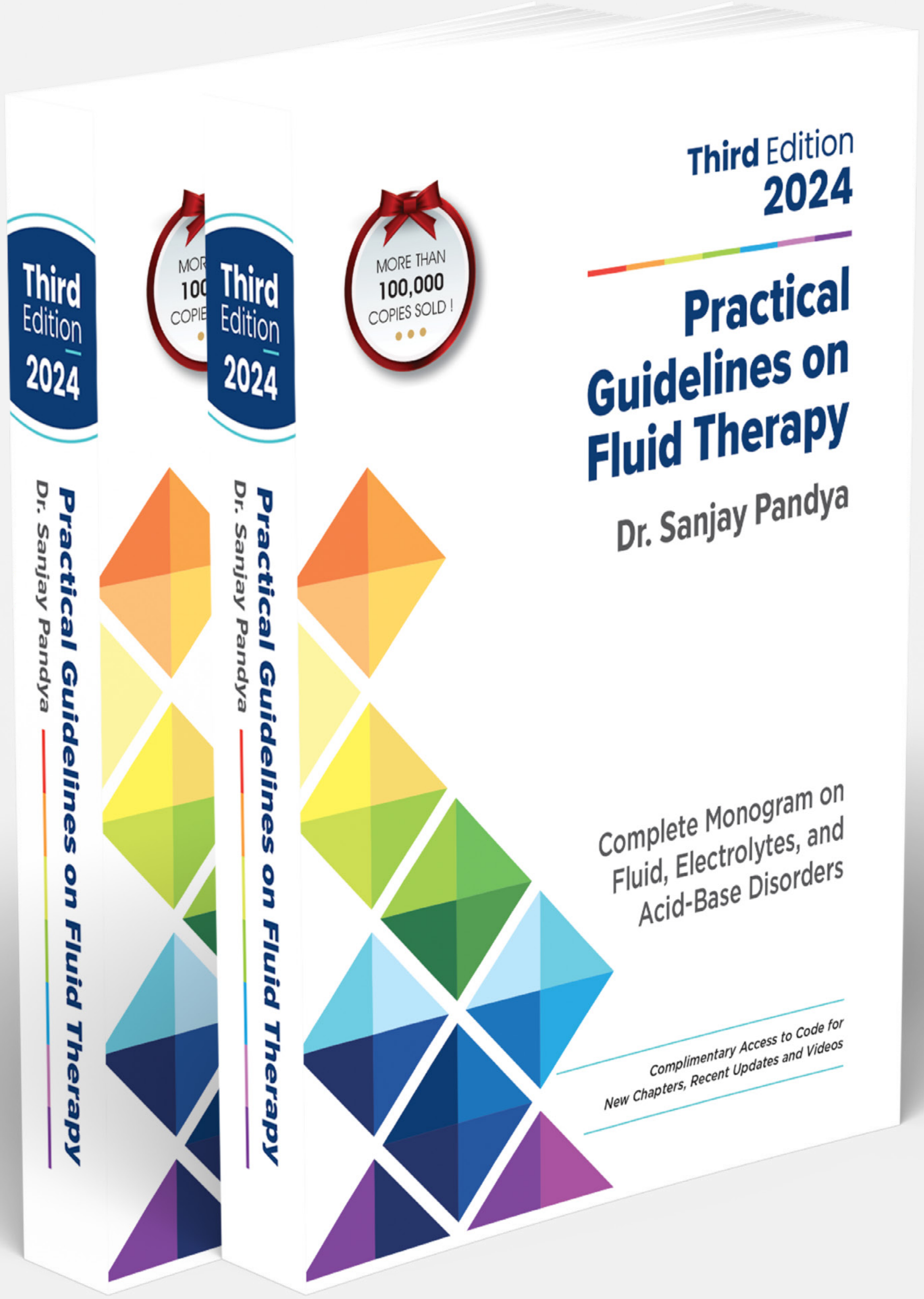
Chapter 5:

Colloid Solutions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Colloids are volume expanders commonly used in clinical practice for fluid resuscitation in hypovolaemic patients. Colloids are electrolyte solutions fortified with large molecular weight molecules that do not pass through semipermeable membranes and therefore are retained within the vascular system. Theoretically, colloids are more effective as plasma volume expanders and improve blood pressure more rapidly than crystalloids because of their intravascular distribution, the property of drawing fluid from extravascular spaces (due to their higher oncotic pressure), and prolonged effect [1, 2].

Compared to crystalloid fluids, colloids are three times more effective in expanding blood volume and increasing cardiac output [3]. So, when plasma or blood is not available immediately, the infusion of colloids to correct circulatory fluid volume is vital and often life-saving in patients with hemorrhagic shock. However, a blood transfusion is subsequently required to maintain the adequate capacity to carry oxygen. The potency of colloid fluids as plasma volume expanders differs with different commercially available colloid fluids, as shown in Table 5.1.

The major advantages and disadvantages of colloids are summarized in Table 5.2 [4]. Colloids vs. crystalloids in resuscitation is a long-standing debate. The colloids were an attractive and preferred choice for resuscitation before a decade [5]. The potential benefits of colloids are greater, rapid, and more prolonged intravascular volume expansion with smaller volume [3, 6–9] and lesser salt and water overload and edema. The benefit of speedier achievement of hemodynamic goals with colloids is less organ damage and a decreased incidence of organ failure [3].

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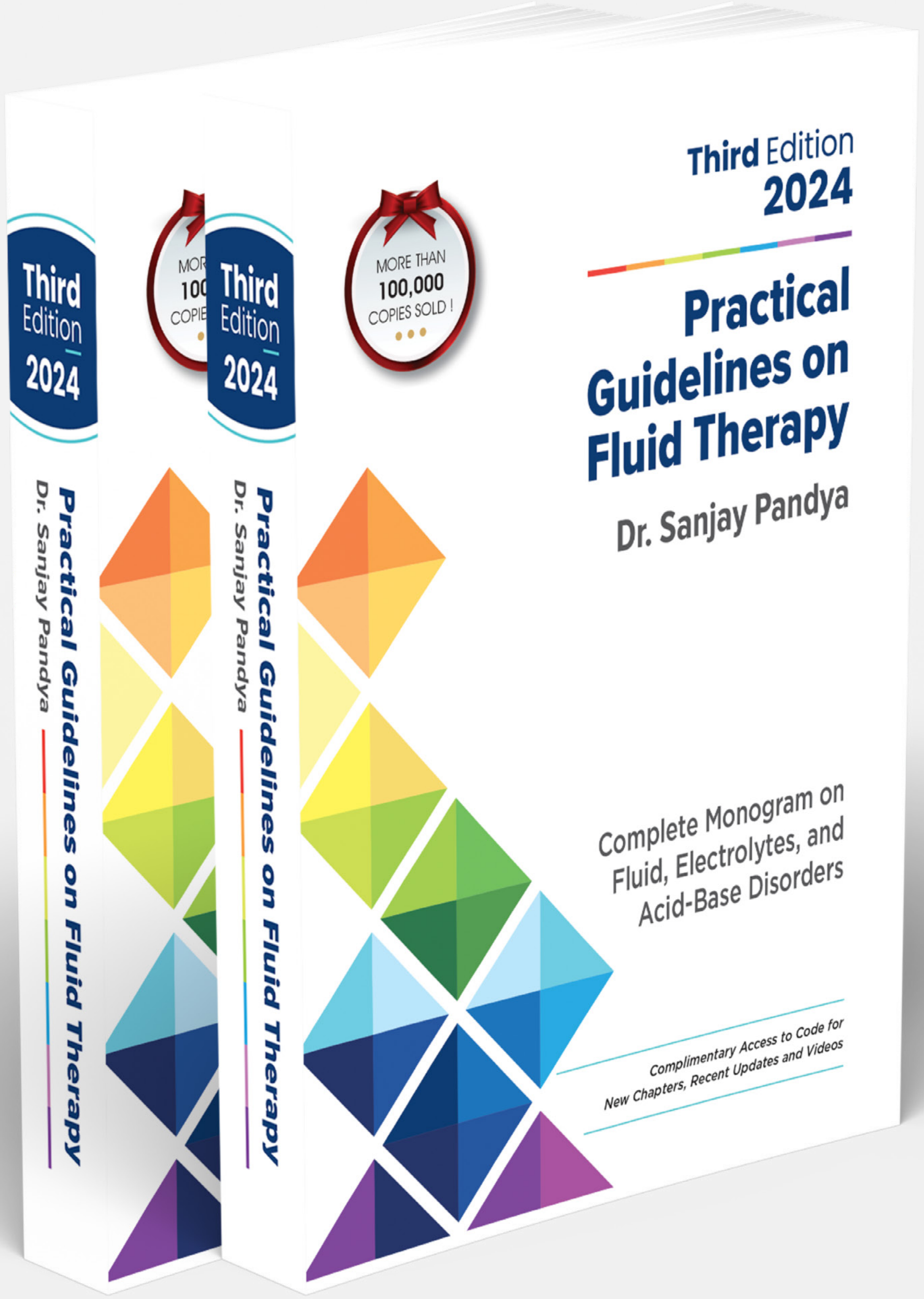
Chapter 6:

Principles, Planning, and Prescribing Fluid Therapy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Principles, Planning, and Prescribing Fluid Therapy

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Fluid administration is commonly needed in hospitalized patients, especially in an emergency, ICU, and surgical units.

Why is it important to plan and prescribe fluid therapy meticulously?

- Fluid administration is an essential and most commonly required intravenous treatment in acutely ill hospitalized patients [1, 2].
- Timely, appropriate, and properly designed intravenous fluid administration is lifesaving [2, 3].
- The prescription plans of fluid therapy vary markedly in different dynamic phases, demanding frequent attention, evaluation, and necessary changes.
- Prescribing intravenous fluids is complex. Unfortunately, doctors' basic knowledge and understanding of prescribing intravenous (IV) fluids are poor, and errors in planning appropriate fluid type, rate, or volume lead to morbidity and mortality, which is preventable [4–7].
- IV fluids are not just an innocent bag of water; their under or over-administration may be potentially harmful [8–11].
- Fluid overload is one of the most common complications of overzealous IV fluid administration, which is often overlooked but is harmful [10, 12–18].

Because of the possibilities of multifactorial errors and harmful effects, it is recommended to use the right type of fluid, in the right volume at the right time, by the right route (in a similar way as using any other pharmacological prescription antibiotics or drugs), and tailor the fluid therapy to meet the patient's individualized needs which reduces the risks and improves the outcome [2, 10, 19, 20].

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Chapter 7:
Maintenance Fluid Therapy

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7 Maintenance Fluid Therapy

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Patients who are euvolemic, hemodynamically stable but unable to take adequate fluid by oral or enteral route need maintenance intravenous (IV) fluids to replace anticipated insensible (such as respiration, perspiration, and stools) and sensible (such as urine) losses [1].

PHYSIOLOGICAL BASIS

The goal of maintenance IV fluid is to replace the ongoing daily physiologic losses such as urine, feces, and sweat, maintain normal water and electrolyte balance and provide adequate calories to avoid starvation ketosis [1, 2].

Ideal maintenance IV fluid should provide adequate water and electrolytes to preserve the extracellular volume and ensure proper tissue perfusion without causing volume depletion, fluid overload, or electrolyte disturbances, along with supplementation for optimal calories [1].

Sodium concentration of maintenance fluids

Sodium concentration of maintenance IV fluids is a crucial but debatable issue discussed in many studies, which needs special consideration because of its two common and potentially harmful effects, hyponatremia [3, 4] and volume overload [5, 6].

How much sodium concentration is appropriate for the maintenance IV fluids in adult patients?

The concepts of appropriate sodium concentration of maintenance IV fluids in adults are changing like a pendulum shift.

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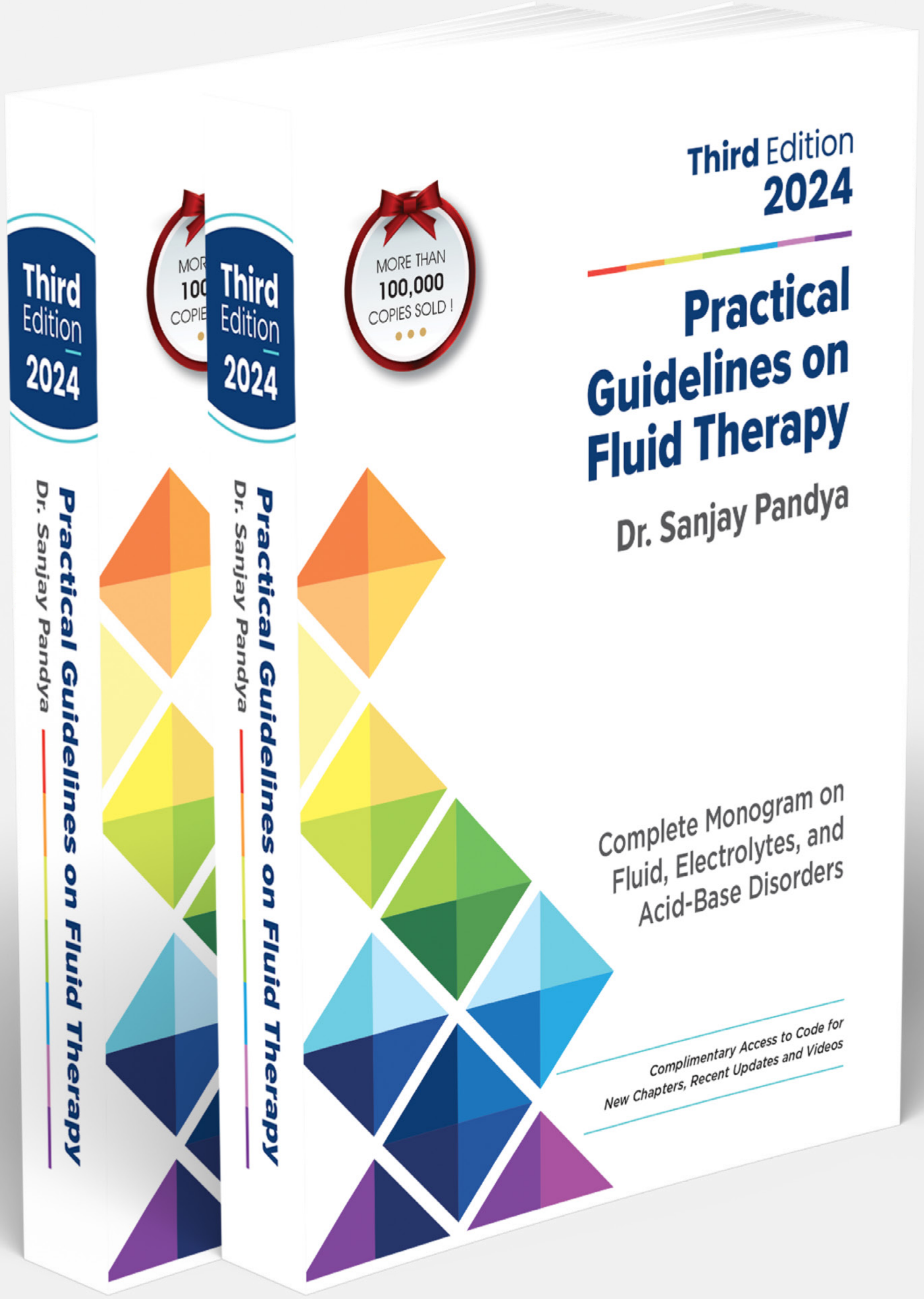
Chapter 8:

Resuscitation Fluids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8

Resuscitation Fluids

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Fluid resuscitation is defined as a rapid administration of intravenous fluids used to restore or maintain a patient's circulatory volume during severe hypovolemia or shock due to significant and sudden fluid or blood losses. The most common indications of fluid resuscitation in critically ill patients are severe hypovolaemia, sepsis, trauma, burn, and perioperative volume loss [1]. The objective of fluid resuscitation is to quickly administer a large fluid volume to restore circulating volume, stabilize hemodynamics, and thereby restore tissue perfusion and oxygen delivery without causing harm due to fluid overload [2]. Identifying the cause of shock and treating it simultaneously is vital.

TIMING AND RATE OF FLUID ADMINISTRATION

Hypovolemic shock is a medical emergency, and fluid resuscitation should begin immediately. Delay in therapy can lead to ischemic injury and possibly to irreversible shock and multiorgan system failure. For initial fluid resuscitation, crystalloid fluids containing 130–154 mEq/L sodium are infused as a bolus of 500 mL within 15 minutes [1, 3]. Usually, one to two liters of fluid is administered rapidly to establish hemodynamic stability, maintain adequate blood flow to organs, and improve tissue perfusion. Fluid resuscitation should be done under close monitoring in high-risk patients who have kidney impairment or congestive heart failure to avoid fluid overload.

As per Surviving Sepsis Campaign recommendations (2021), in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 hours [4]. The use of an average fluid volume of around 30 mL/kg was supported by the PROCESS [5], ARISE [6], and PROMISE trials [7], where patients, on average, received this volume of fluid before randomization.

As early aggressive fluid resuscitation with large-bore IV cannulas is crucial in severe sepsis and septic shock, fluid resuscitation should be initiated earliest (after obtaining blood for measuring lactate and blood cultures) and should be completed within the first 3 hours. Earlier fluid resuscitation (within the first 3 hours) improves survival in patients with severe sepsis and septic shock [4]. Delayed administration of fluid (>2 hours after diagnosis) is the most crucial predictor of the fluid refractory state, which is associated with longer hospital stays and higher mortality [8].

If the patient does not respond to adequate fluid resuscitation, consider using vasopressors and inotropes and rule out other causes of shock besides hypovolemia (e.g., cardiogenic shock, sepsis) [9]. Consider earlier use of vasopressors in patients at risk of volume overload and to achieve the initial mean arterial pressure (MAP) target more rapidly.

An initial target of fluid resuscitation is to achieve a mean arterial pressure (MAP) of 65 mmHg [4]. Following initial fluid resuscitation, additional fluid infusion is planned based on a frequent assessment of clinical parameters, hemodynamic status, and laboratory tests.

The requirement for IV fluids changes over time. During the early salvage phase of shock (0–24 h), rapid fluid replacement in an adequate volume is essential. Fluid requirements decrease subsequently during optimization and stabilization phases (24–96 h), so the volume of fluids infusion should be reduced. Restrictive strategy during the last de-escalation phase (>96 h) is associated with better outcomes [10, 11].

TYPE OF FLUIDS FOR RESUSCITATION

The choice of resuscitation fluid depends on the severity and etiology of hypovolemic shock. Three major categories of fluids used for resuscitation are crystalloid fluids (normal saline, Ringer's lactate, and other chloride-restrictive balanced crystalloids such as Plasma-Lyte); colloids (albumin, hydroxyethyl starch (HES), dextran, and gelatine), and blood products (packed red blood cells).

THE PHYSIOLOGY OF FLUID SELECTION

Understating the basic physiology of the distribution of infused fluids helps in the selection of appropriate fluid for a given patient. When different IV fluids are infused, their distribution in various compartments of body fluids differs depending upon their composition (Table 8.1 and Figure 8.1). The ability of infused IV fluids to expand intravascular volume determines its effectiveness in raising blood pressure.

Avoiding 5% dextrose in the treatment of hypovolemic shock: 5% dextrose is typically avoided in the treatment of hypovolemic shock for several reasons:

1. **Poor expansion of intravascular volume:** 1000 ml of 5% dextrose increases the extracellular fluid (ECF) volume by only 330 ml, with just 83 ml (or 1/4 of the ECF) remaining in the intravascular space [12]. As 1 liter of 5% dextrose will increase the

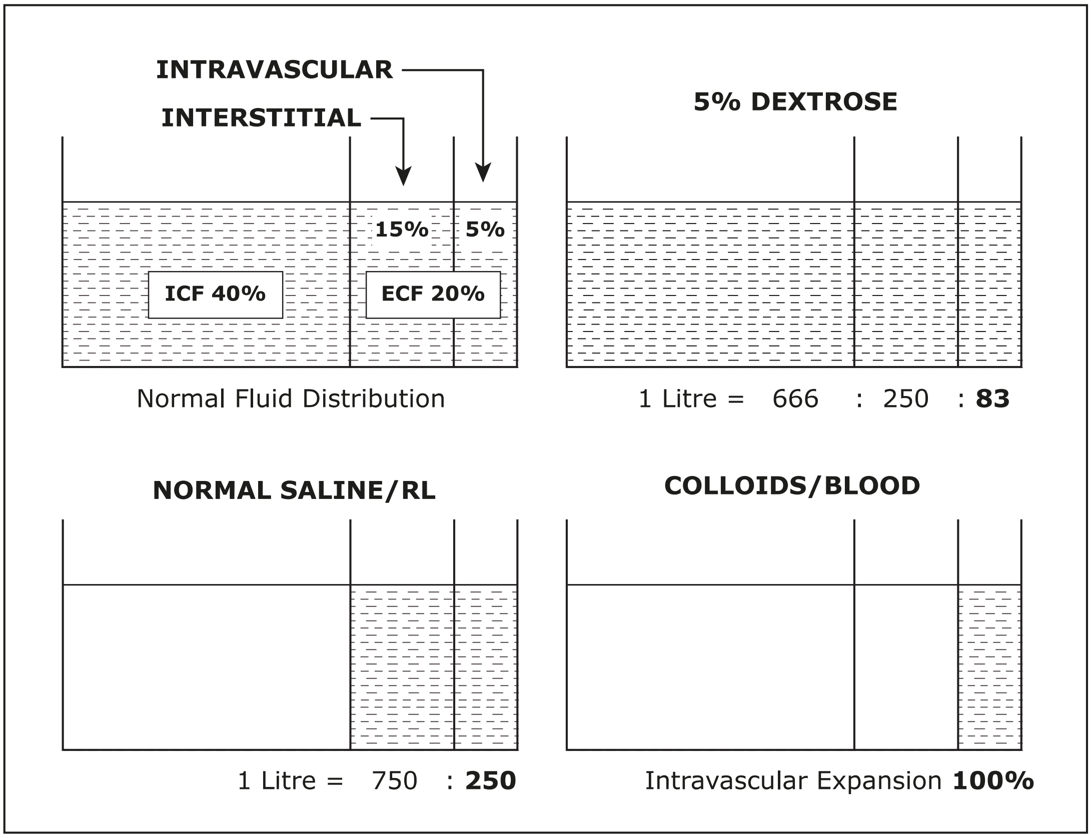
INTRAVASCULAR
INTERSTITIAL
15%
5%
ICF 40%
ECF 20%
Normal Fluid Distribution
5% DEXTROSE
1 Litre = 666 : 250 : 83
NORMAL SALINE/RL
1 Litre = 750 : 250
COLLOIDS/BLOOD
Intravascular Expansion 100%

Figure 8.1 Distribution of IV solutions in different fluid compartments.

Table 8.1 Distribution of IV solutions in body fluid compartments

Fluid distribution (1000 ml)	5% Dextrose	0.45% Saline	RL and 0.9% saline	Colloids/Blood products
Intracellular fluid (ml)	667	333	0	0
Extracellular fluid (ml)	333	667	1000	1000
Interstitial fluid (ml)	250	500	750	0
Intravascular fluid (ml)	83	167	250	1000

intravascular volume only by about 83 ml (8%), the rise in blood pressure will be poor in the patient with shock.

2. **Increased urine output due to osmotic diuresis:** Administering a large volume of 5% dextrose at a faster rate results in a glucose load of more than 25 gm/hour, inducing osmotic diuresis. So, even in the presence of hypovolemia, there will be increased urine output, which delays the correction of dehydration.

   Increased urine output will also create a false impression that the fluid deficit has been resolved. In such a setting, the rate of fluid replacement may be slowed down despite hypovolemia; therefore, hypotension may not improve. So, 5% dextrose should be avoided in the treatment of shock.

Selecting normal saline and Ringer's lactate as initial fluids for treating Hypovolemic shock: Crystalloid fluids such as normal saline and Ringer's lactate are sodium-rich electrolyte solutions and therefore are distributed only in the ECF compartment (25% in intravascular and 75% in interstitium). Infusion of 1 liter of these fluids will expand intravascular volume by about 250 ml, so the blood pressure rise will be much more rapid compared to 5%-dextrose [13].

As normal saline, Ringer's lactate and other chloride-restrictive balanced crystalloids are dextrose-free in an emergency when the patient's glycemic status is unknown; these fluids are safe for initial resuscitation. Moreover, compared to colloids, these fluids are inexpensive, readily available, noninfectious, reaction-free, and easy to store, so they are preferred for the initial treatment of shock.

The use of dextrose saline infusion for fluid resuscitation: Avoid using dextrose saline infusion for fluid resuscitation. 1000 ml of Dextrose saline contains 50 gm of dextrose (5% dextrose) and 154 mEq of sodium and chloride (0.9% NaCl). Faster infusion of fluid with 5% dextrose will cause hyperglycemia and resultant osmotic diuresis and increased urine output. Increased urine output in the presence of hypovolemia delays the correction of dehydration, which is not desirable. Therefore, all dextrose-containing fluids are not appropriate for fluid resuscitation [14].

Colloids and blood products: the most potent options for rapidly raising blood pressure during shock: For the prompt rise of blood pressure in shock, natural colloids (such as albumin), synthetic colloids (such as hydroxyethyl starches, gelatin solutions, and dextran), and blood products are more potent agents.

Large molecules of these agents do not readily cross the capillary membrane and, therefore, are primarily restricted to the intravascular compartment. In contrast to normal saline, where 3/4 of it enters the interstitium, the total volume of infused colloids and blood products remains in the vascular space. As 100%

of the infused volume stays in the vascular space and selectively expands the plasma volume, they will raise blood pressure rapidly.

Colloids carry a lesser risk of pulmonary edema since the increase in plasma oncotic pressure favors fluid movements out of the interstitium into the vascular space.

Despite the physiological potency and benefits of colloids, they are not the preferred or superior solution over crystalloids in clinical practice, as discussed later.

SELECTING IV FLUID FOR RESUSCITATION

From a variety of available choices, to choose the appropriate fluid for resuscitation, consider the composition, effectiveness, benefits, and disadvantages of different solutions. Three common IV replacement fluids used to manage hypovolemic shock are crystalloids, colloids, and blood products:

- **Crystalloids:** The most widely used first-line therapy in managing hypovolemic shock comprises crystalloids such as normal saline, Ringer's lactate, and PlasmaLyte.
- **Colloids:** Colloids are second-line resuscitation therapy used in selected patients with hypotension. Among colloids, the use of natural colloids like albumin, which is safe but highly expensive, is recommended in specific clinical settings. However, the use of synthetic colloids such as hydroxyethyl starch, dextran, and gelatin is not recommended, and they are avoided or discouraged due to their harmful effects and lack of benefits.
- **Blood Products:** Packed red blood cells or blood substitutes are essential for effective resuscitation for patients with significant blood loss or anemia associated with hypotension.

Each type of fluid comes with its characteristics and is chosen based on the specific needs and conditions of the patient.

CRYSTALLOID RESUSCITATION: FIRSTLINE THERAPY

Crystalloids like Normal saline and balanced crystalloids like Ringer's lactate and PlasmaLyte are the most frequently prescribed crystalloid solutions for resuscitation.

The selection between normal saline and balanced crystalloids depends on their respective clinical benefits and safety profiles, not solely on physiological characteristics. This choice remains a subject of ongoing controversy. To provide a clear and comprehensive understanding of the appropriate use of crystalloids, key studies, and guidelines that provide comparative insights are summarized below:

- Composition of commonly used IV crystalloids.
- Physiological basis, advantages, disadvantages, and preferred indications for using normal saline and balanced crystalloids.
- A literature review to address the ongoing controversy between saline and balanced crystalloids.
- Conclusions and current recommendations for appropriate use of crystalloids.

The composition of commonly used IV crystalloids

Understanding the composition of commonly used IV crystalloids is crucial

Table 8.2 Composition of plasma and IV crystalloid resuscitation fluids

	Na^+ mEq/L	K^+ mEq/L	Cl^- mEq/L	Acet. mEq/L	Lact. mEq/L	Ca^{2+} mEq/L	Mg^{2+} mEq/L	Gluc. mEq/L	Osm. mOsm/L	SID mEq/L
Plasma	136–145	3.5–5.0	98–106	-	-	2.2–2.6	0.8–1.0	-	285–295	40
0.9% NaCl	154	-	154	-	-	-	-	-	308	0
RL	130	4.0	109	-	28	3.0	-	-	273	28
PlasmaLyte	140	5.0	98	27	-	-	3.0	23	295	50
Sterofundin	145	4.0	127	24	-	5.0	2.0	-	309	29

Acet.: Acetate; Ca^{2+}: Calcium; Cl^-: Chloride; Gluc.: Gluconate; Lact.: Lactate; Mg^{2+}: Magnesium; Osm.: Osmolality; K^+: Potassium; Na^+: Sodium; SID: Strong ion difference

for their appropriate use in resuscitation; a comparison of these compositions with human plasma is summarized in Table 8.2.

A. Normal saline

Isotonic saline, or 0.9% saline (0.9% NaCl), often referred to as "normal saline", is among the most commonly used crystalloids for resuscitation worldwide. Below are the advantages and disadvantages of using normal saline.

Advantages

Major advantages of normal saline for resuscitation include:

- **Availability and compatibility:** It is readily available, cost-effective, and compatible with the co-infusion of blood products and medications like ceftriaxone [15].
- **Volume expansion:** With 154 mEq/L of sodium, it effectively expands intravascular volume and corrects hypotension.
- **Safe for specific conditions:** It is the preferred option for patients with brain injury, hypochloremia, hypovolemic hyponatremia, and metabolic alkalosis. As the osmolarity of normal saline is 308 mOsm/L (compared to normal plasma osmolality of about 285 mOsm/kg), its use for resuscitation in neurological patients is without the risk of cerebral edema.
- **Glucose-free:** Ideal for scenarios with unknown glycemic statuses due to its lack of glucose content.

Disadvantages

The use of normal saline can be harmful, as it is neither "normal" nor "physiological" [16]. Major disadvantages of normal saline for resuscitation include:

Nonphysiological composition: Normal saline differs from the balanced crystalloid Ringer's lactate in three key aspects:

1. It has a significantly higher chloride concentration (154 versus 109 mEq/L).
2. It lacks a buffer, essential for maintaining pH.
3. It does not contain several electrolytes, like potassium and calcium, that are present in plasma.

Harmful effects: Normal saline contains supraphysiologic chloride concentrations (154 mEq/L) -50% higher than human serum chloride concentration [17]. The infusion of large volumes of this high chloride-containing fluid can lead to hyperchloremic acidosis [18, 19], an increased risk of acute kidney injury [18, 20], a greater need for renal replacement therapy, higher hospital mortality [21–23], coagulopathy [24], hyperkalemia, and more pronounced interstitial fluid retention [25].

Hyperchloremic metabolic acidosis

Infusing a large volume of normal saline often results in a normal anion gap hyperchloremic metabolic acidosis [26, 27]. This effect can be attributed to factors such as the strong ion difference (SID), reduced bicarbonate (HCO3) reabsorption, and dilution of bicarbonate [28]:

- The SID of normal saline is zero; therefore, its infusion decreases plasma SID, leading to metabolic acidosis (SID: Normal value = 40; Normal saline = 0; RL = 28, PlasmaLyte = 50) [16, 29].
- Administering a large volume of normal saline reduces renal bicarbonate reabsorption, decreasing bicarbonate levels [30].
- Using large volumes of bicarbonate-free fluids like normal saline dilutes the bicarbonate concentration in the body, inducing dilutional acidosis [2, 31].

Risk of acute kidney injury (AKI)

Administering a large volume of normal saline can lead to hyperchloremia and an increase in chloride concentration in the distal tubular fluid. This elevated chloride level is sensed by macula densa cells located in the distal convoluted tubule. These tubular cells then transmit signals to the afferent arterioles, triggering vasoconstriction (known as "Tubuloglomerular Feedback"). This vasoconstriction, in turn, diminishes renal perfusion and reduces the glomerular filtration rate (GFR), potentially leading to acute kidney injury [16, 20, 27, 32, 33].

Use in hyperkalemia

Infusing a large volume of normal saline can induce hyperchloremic metabolic acidosis, promoting the shift of potassium out of cells and potentially causing or worsening hyperkalemia. So, the simple logic that normal saline, because it does not contain potassium, is safe to use in hyperkalemia is a myth. On the contrary, Ringer's lactate does not cause any acidosis, and in a patient with hyperkalemia, it will actually lower his serum potassium level and, therefore, is safe. Thus, Ringer's lactate is often preferred over normal saline in cases of hyperkalemia [34–36].

B. Balanced crystalloids

Emerging evidence suggests that using normal saline as a resuscitation fluid leads to complications like hyperchloremic metabolic acidosis, AKI, etc. Balanced crystalloids (buffered or chloride-restrictive solutions or balanced salt solutions) are the result of a search for safer fluid for resuscitation. Balanced crystalloids are more physiological than normal saline and are increasingly advocated as a first-line resuscitation fluid [15].

To provide a comprehensive overview of RL's optimal use, the sections below outline its basic physiology, benefits, applications in various electrolyte and clinical disorders, and potential disadvantages.

Balanced electrolyte composition

Balanced crystalloid solutions are formulated to closely mirror the electrolyte composition, osmolality, and pH of human plasma, enabling the administration of large volumes without the risk of electrolyte disturbances.

Provides buffer to prevent or correct metabolic acidosis

Balanced crystalloids contain precursors of bicarbonate (e.g., lactate and acetate) that are metabolized into bicarbonate, helping to correct metabolic acidosis [37–39]. This buffering effect is a significant advantage over normal saline, which lacks this buffering capacity. Since bicarbonate-containing solutions are unstable in plastic containers, alternative metabolizable anions like lactate, acetate, gluconate, and malate are used to formulate balanced crystalloids to ensure stability and efficacy.

Reduces the risks of hyperchloremia

Balanced crystalloid solutions containing significantly less chloride than normal saline, effectively reduce the incidence of an increase in plasma chloride levels [40]. The potential benefit of balanced crystalloid solutions comes from their lower chloride content (<112 mEq/L) and a strong ion difference (SID) that closely matches that of human plasma. The chloride concentrations in Ringer's lactate (109 mEq/L) and PlasmaLyte A (98 mEq/L) are similar to that of human plasma (102 mEq/L), contrasting with the high chloride concentration in normal saline (154 mEq/L) [41, 42].

Effect of RL on serum lactate levels

Despite each liter of Ringer's lactate containing 28 mmol of sodium lactate, its infusion in hemodynamically stable adults only transiently elevates lactate levels or does not significantly increase them compared to normal saline solution [43–46]. As the rise in serum lactate levels is very minimal (<1.00 mmol/L) following the infusion of RL, it may not significantly interfere with the interpretation of serial lactate measurements as an index of the severity of acidosis [44, 47].

Use in lactic acidosis misconceptions and facts

Contrary to a common misconception, the infusion of Ringer's lactate does not induce lactic acidosis. The avoidance of this solution due to fears of exacerbating lactic acidosis is based on a misunderstanding.

Clarification is needed regarding the difference between lactic acid and the sodium lactate contained in Ringer's lactate. Remember that lactic acid, consisting of anion lactate plus cation hydrogen and with a pH of 2.44 to 3.51, is an "acid", and it's harmful.

However, the sodium lactate in Ringer's lactate, a "conjugate base" consisting of anion lactate and cation sodium with a pH of 6.0 to 7.3, is benign, contrasting the harmful nature of lactic acid. So, in conclusion, interestingly, RL not only has the capacity to absorb hydrogen ions, potentially correcting acidosis or leading to metabolic alkalosis, but also, importantly, it does not cause lactic acidosis [48, 49].

Safety in hyperkalemia

Ringer's lactate contains 4 mEq/L potassium, whereas the potassium content of normal saline is zero. The common apprehension that potassium-containing Ringer's lactate is unsafe and should be avoided in patients with hyperkalemia is a myth [35, 50]. As the potassium concentration of Ringer's lactate is just 4 mEq/L, its administration cannot raise the value of serum potassium higher than its potassium concentration (i.e., 4 mEq/L) and, therefore, cannot lead to hyperkalemia. In contrast, the low potassium content in Ringer's lactate may cause the potassium level of a hyperkalemic patient to trend toward 4 mEq/L [51, 52].

98% of potassium is distributed within the intracellular compartment, and serum potassium levels are significantly influenced by a change in pH that shifts potassium. Acidosis triggers a shift of potassium from the intracellular fluid (ICF) to the extracellular fluid (ECF). Since Ringer's lactate rectifies acidosis, it not only prevents hyperkalemia but can actually reduce serum potassium levels, supporting its safety for patients with hyperkalemia. So, we can conclude that Ringer's lactate is safer than normal saline in hyperkalemia [34, 36, 52].

Safety in neurological disorders

RL is a hypotonic fluid with a plasma osmolarity of 273 mOsm/L, lower than the normal plasma osmolality of about 285 mOsm/kg. Because of its hypotonicity, RL can cause or exacerbate cerebral edema and should, therefore, be avoided in cases with a risk of raised intracranial pressure, such as aneurysmal subarachnoid hemorrhage (aSAH), traumatic brain injury (TBI), and in patients undergoing neurosurgery [53–56].

Use in liver disorders

The lactate in RL is primarily metabolized into bicarbonate in the liver. The administration of RL is not an absolute contraindication for patients with liver dysfunction or cirrhosis, and its clinical impact remains unknown [57–59]. However, for those with severe or frank liver failure or post-liver transplantation, where a significant reduction in lactate metabolism is observed, bicarbonate-buffered solutions are often preferred over lactate-buffered ones [47, 60]. Balanced crystalloids, like PlasmaLyte, contain acetate instead of lactate, and acetate metabolism occurs in all body tissues and is not limited to liver tissues. So, PlasmaLyte can be used instead of RL in severe liver diseases.

Caution: Metabolic alkalosis can occur in patients with severe liver failure and cirrhotic patients due to vomiting, nasogastric suction, diuretics, and hypovolemia. It can promote ammonia production and predispose the development of hepatic encephalopathy. Therefore, balanced fluids that provide buffers and can aggravate metabolic alkalosis should be avoided in such patients.

Use in diabetic ketoacidosis

RL may be considered over normal saline for treating patients with diabetic ketoacidosis (DKA) because it is dextrose-free and reduces the risk of hyperchloremic metabolic acidosis. Additionally, it provides bicarbonate to correct acidosis and offers other benefits such as lower total cost, shorter hospital stays, and quicker, more efficient resolution of acidosis [61–65].

Precautions

Large volumes of balanced crystalloids may result in hyperlactatemia, metabolic alkalosis, and hypotonicity. As the osmolality of RL is low compared to plasma (273 vs. 290 mOsm/L), RL may exacerbate cerebral edema and therefore avoided in head injury and brain edema. As the capacity of the liver to metabolize lactate and generate bicarbonate is impaired in severe liver failure, the use of RL is avoided in such patients. Since Ringer's lactate contains calcium, it may not be suitable for co-infusion with blood products through the same IV line [15].

C. Saline vs. balanced crystalloids: A review of literature

To resolve the dilemma of choosing between normal saline and balanced crystalloids, establish the superiority of one fluid over the other, and provide evidence-based insights, we conducted an extensive review and analysis of various clinical trials, meta-analyses, and society guidelines. In this comprehensive review, evidence is categorized based on the superiority of each fluid, findings indicating no significant difference between the two, and insights from meta-analyses and society guidelines; a summary of conclusions and current recommendations is provided below.

1. Trials suggestive of the superiority of balanced crystalloids

- Shaw et al. (Ann Surg 2012) compared adult patients undergoing major open abdominal surgery who received either normal saline (30,994 patients) or a PlasmaLyte (926 patients) on the day of surgery. This study concluded that PlasmaLyte was associated with less postoperative morbidity than normal saline [66].
- Yunus et al. (JAMA 2012) compared the association of a chloride-restrictive vs. chloride-liberal IV fluid strategy with AKI in 760 critically ill patients. This study concluded that the chloride-restrictive strategy in a tertiary ICU was associated with a significant decrease in the incidence of AKI and the use of RRT [20].
- McCluskey et al. (Anesth Analg 2013) compared the impact of postoperative hyperchloremia in 22,851 patients undergoing noncardiac surgery. This study concluded that postoperative hyperchloremia was associated with increased mortality, renal dysfunction, and length of hospital stay [67].
- Raghunathan et al. (Crit Care Med 2014) compared the outcome after resuscitation with balanced versus non-balanced fluids in 53,448 patients with sepsis in an ICU. This study concluded that among critically ill adults with sepsis, resuscitation with balanced crystalloids was associated with a lower risk of in-hospital mortality [68].
- SMART Trial (Semler et al. NEJM 2018) is a very large study that compared normal saline with balanced crystalloids among 15,802 critically ill adults. This study concluded that using balanced crystalloids resulted in a lower rate of death from any cause, RRT, or persistent renal dysfunction than using saline [69].
- SALT-ED Trial (Self et al. NEJM 2018) compared normal saline with balanced crystalloids among 13,347 noncritically ill adults. This study concluded that there was no difference in hospital-free days between both groups, but the use of balanced IV fluid resulted in a lower rate of death from any cause, RRT, or persistent renal dysfunction than the use of saline [70].

2. Trials and analysis suggestive of no difference between both groups

- The SPLIT Trial (Young et al. JAMA 2015) compared normal saline with PlasmaLyte in 2278 ICU patients and concluded that using a buffered crystalloid compared with saline did not reduce the risk of AKI [71]. A major limitation of this study was the median administration of a small volume of saline (<2 liters) and, therefore, a lesser risk of developing hyperchloremia.
- The SALT Trial (Semler et al. Am J Respir Crit Care Med 2017) compared normal saline with balanced crystalloids in 974 ICU patients and concluded no difference in the overall incidence of AKI or major adverse kidney events [72].
- The BaSICS Trial (Zampieri et al. JAMA 2021), a multicenter, double-blind RCT involving 11,000 patients, compared normal saline with balanced crystalloids and concluded that there were no significant differences in mortality rates or AKI incidence [73].

- The PLUS Study (Finfer et al. NEJM 2022), a multicenter, double-blind RCT involving 5,000 patients, compared normal saline to balanced crystalloids and concluded that the balanced crystalloid group did not demonstrate reduced mortality or kidney injury [74].

3. Meta-analysis and society guidelines

- Krajewski et al. (Br J Surg 2015) reported in a meta-analysis of 21 studies involving 6,253 patients that the use of high-chloride fluids in perioperative or intensive care settings was associated with an increased risk of acute kidney injury, with no observed benefits on mortality [32].
- Cochrane Database Syst Rev. (2017) reported that perioperative administration of buffered versus non-buffered crystalloid fluids showed insufficient evidence of impacting mortality and organ system function but noted a significant reduction in postoperative hyperchloremia and metabolic acidosis with the use of buffered fluids [75].
- Surviving sepsis campaign guidelines (Evans et al. Crit Care Med 2021): The guidelines advise using crystalloids for both initial resuscitation and ongoing intravascular volume replenishment in adult patients with sepsis and septic shock [4]. The previous Surviving sepsis guidelines (2017) [76] suggested using either balanced crystalloids or saline, but in 2021, guidelines suggested using balanced crystalloids instead of normal saline for resuscitation [4].
- Hammond NE et al. (NEJM Evid 2022) conducted a Systematic Review with Meta-Analysis comparing balanced crystalloids to saline in critically ill adults and demonstrated reduced mortality in patients who received balanced crystalloids [77].
- Beran A et al. (J Clin Med 2022) demonstrated in their systematic review and meta-analysis that adults with sepsis treated with balanced crystalloids showed reduced mortality and AKI compared to those who received normal saline [78].
- Isha et al. (Front Med 2023) conducted a retrospective analysis that compared normal saline with balanced crystalloids in 2022 patients and found no significant difference in mortality rates, hospital stay, ICU admission rates, mechanical ventilation needs, oxygen therapy, and renal replacement therapy [79].
- Zampieri et al. (Lancet Respir Med. 2024) conducted a systematic review and meta-analysis, demonstrating lower in-hospital mortality associated with the use of balanced solutions compared to saline in the ICU [80].
- European Society of Intensive Care Medicine (ESICM) clinical practice guideline (Intensive Care Med. 2024): Recent ESICM Guidelines recommends the use balanced crystalloids instead of normal saline for resuscitation in severe volume depletion or hypovolemic shock in critical patients, and in patients with sepsis or kidney injury [56].

Various systematic reviews with meta-analyses and guidelines [4, 32, 56, 75, 77, 78, 80], except the recent one performed by Isha et al. on a small number of patients [79], suggesting that using balanced crystalloids offers some benefits compared to normal saline.

4. Trials suggestive of the superiority of normal saline

- To date, not a single study has demonstrated the superiority of saline over balanced crystalloids in the selection of appropriate resuscitation fluids. The absence of evidence establishing the superiority of saline indirectly reinforces the preference for using balanced crystalloids. This is consistent with the existing body of evidence highlighting the efficacy of balanced crystalloids in fluid resuscitation, even in the absence of high-quality reference evidence.

D. Crystalloids: conclusions and current recommendations

There is no clear consensus on recommending one crystalloid over others [81, 82]. However, suggestions are made based on the literature, as mentioned earlier, and various recent studies. However, it's crucial to acknowledge that the preference for using balanced crystalloids is without high-quality evidence [76, 83]. Given the low risk of harm and the real possibility of benefit, the use of balanced crystalloids could be a prudent choice in clinical practice [84]. Selecting resuscitation fluids considering history, cause, acid-base, and electrolyte disorders will be wise.

1. Balanced crystalloids preferred firstline modality

- The current trend in literature, including the recent Surviving Sepsis Campaign guideline (2021) and the European Society of Intensive Care Medicine fluid therapy guideline (2024), favors the use of isotonic, balanced crystalloids as the preferred resuscitation fluids [56, 69, 85–97]. The benefits of using balanced crystalloids are more evident in patients with sepsis, metabolic acidosis, hyperchloremia, increased creatinine, or those at risk of kidney injury [4, 56, 98].
- Ringer's lactate is suggested as the preferred resuscitation fluid in sepsis [37, 42, 84], acutely ill critical patients [99–101], surgical patients [66, 102], trauma [103, 104], high risk for acute kidney injury [105], acute pancreatitis [106–108], diarrhea, burns [109]. Benefits of balanced solutions are more evident when administering fluid in large volumes, particularly for septic patients [110, 111].
- Patients with metabolic acidosis should receive balanced crystalloids with an "alkalinizing" effect, while patients with metabolic alkalosis and hypochloremia should be treated with normal saline [112].
- Ringer's lactate should be avoided or used with caution in patients with severe metabolic alkalosis and hypochloremia (e.g., due to profound vomiting) [18], those with frank hepatic failure [113], and individuals with traumatic brain injury or at risk of increased intracranial pressure [18, 53].
- Although lactate metabolism may be impaired in patients with severe lactic acidosis, sepsis, or liver failure, Ringer's lactate does not cause or aggravate lactic acidosis [49, 50].
- Besides the fact that balanced crystalloids contain a small amount of potassium, the risk of hyperkalemia is significantly lower compared to normal saline [18, 35, 50].

2. Normal saline: selective use preferred

- Infusion of large quantities (>2 L) of supraphysiologic chloride containing normal saline can cause hyperchloremic metabolic acidosis, acute kidney injury [114], coagulopathy, increased hemodynamic instability, and potential mortality and therefore is harmful [115].

- Avoid administering large volumes of chloride-rich normal saline to all patients, especially those at high risk for AKI or incipient AKI, due to the potential risk of acute kidney injury [105, 116].
- Small to moderate amounts of normal saline do not increase the incidence of acute kidney injury [71]. Thus, modest volumes of normal saline can be administered to patients with normal kidney function in the absence of hyperchloremia and sepsis [117–119].
- Normal saline is the fluid of choice for patients with metabolic alkalosis, hypovolemia due to vomiting or upper gastrointestinal suction, traumatic brain injury, and those receiving blood products [18, 39, 56, 90, 112–122].

SELECTION OF BALANCED CRYSTALLOID

The evidence supporting the use of balanced crystalloid solutions as preferred resuscitation fluids over saline is growing [1]. In addition to Ringer's lactate, other newer balanced crystalloids like PlasmaLyte, Sterofundin, and Ringer's acetate are commercially available. Table 8.2 provides a detailed comparison of the composition of these balanced crystalloids with the body's natural serum concentrations. However, selecting the appropriate one for practical use presents a dilemma. To choose the most suitable balanced crystalloid, considerations include:

- Understanding the difference between lactate and Acetate buffer.
- Physiological basis for limitations of Ringer's lactate.
- Understanding the composition of PlasmaLyte and its advantages.
- Evidence comparison of Ringer's lactate vs. PlasmaLyte.
- Summary and clinical indications of newer balanced crystalloids.

A. Understanding the difference between lactate and acetate buffer

Balanced crystalloids contain lactate and acetate as buffers and provide bicarbonate. Lactate is primarily metabolized in the liver, a process that can be impaired in patients with substantial liver dysfunction, extreme hypoxia, severe sepsis and septic shock, or tissue hypoperfusion due to any form of pronounced hypotension [123, 124]. In contrast, acetate is metabolized in tissues throughout the body, not just the liver, making it a more adaptable choice for patients with severe liver dysfunction [42, 125]. Importantly, metabolizing capacity of acetate is preserved in shock [39, 126]. Additionally, acetate is rapidly converted into bicarbonate and doesn't require significant oxygen, enhancing its suitability for diverse patient populations [42, 125].

B. Physiological basis for limitations of Ringer's lactate

Ringer's lactate remains the default choice among balanced crystalloids and is widely used as an effective resuscitation fluid in various clinical scenarios. However, certain compositional characteristics can make it a less suitable choice for specific patient populations. These limitations are associated with its:

- Use of lactate as a buffer: In cases of severe liver impairment, hypoxia, acidaemia, or shock, the body's ability to convert lactate into bicarbonate is compromised [123, 124]. This impairment leads to not only a lack of buffering benefits but also lactate accumulation and a rise in serum lactate levels [44]. Consequently, using lactate levels as markers for resuscitation effectiveness becomes challenging.

- Lower osmolality: As RL is a hypotonic fluid (osmolality of RL 278 mOsmol/L vs. plasma osmolality 290 mOsmol/L), use it with caution in neurological patients with cerebral edema [39].
- Lower sodium content: Since RL contains less sodium than plasma (130 mEq/L vs. 140 mEq/L serum sodium), administering it in large volumes can lead to hyponatremia.
- Calcium content: The presence of calcium in RL can lead to precipitation when mixed with citrate in blood transfusions [15].

C. Understanding the composition of PlasmaLyte and its advantages

The growing preference for PlasmaLyte is attributed to its unique composition, which closely mimics human plasma in terms of electrolyte content, osmolality, and pH [127]. The advantages of PlasmaLyte include not only the correction of volume and electrolyte deficits but also the improvement of acidosis. Here are the key compositional features that determine its benefits, as discussed below:

- Use of acetate as a buffer in PlasmaLyte: PlasmaLyte replaces the lactate in RL with anions like acetate, gluconate, and maleate as bicarbonate precursors. Acetate's ability to be metabolized both in the liver and other tissues of the body allows it to ensure the conversion to bicarbonate even in severe liver failure and shock [42, 125]. PlasmaLyte has better buffering agents and effects. Furthermore, PlasmaLyte doesn't affect serum lactate levels, ensuring accurate readings during shock.
- Osmolality equal to plasma: PlasmaLyte, having an osmolality equal to plasma (290 mOsmol/L), does not carry the risk of causing cerebral edema, unlike hypotonic fluids.
- Sodium concentration similar to plasma: The sodium concentration in PlasmaLyte is identical to that of plasma (140 mEq/L), reducing the risk of hyponatremia or hypernatremia during large-volume fluid infusion [42].
- Free of calcium content: Being free of calcium, PlasmaLyte mitigates the risk of calcium overload and avoids complications associated with the co-administration of blood products containing citrate, which can lead to calcium precipitation.
- Magnesium content: Hypomagnesemia is common in critically ill patients, and PlasmaLyte, containing 1.5 mmol/L of magnesium, can be beneficial in these cases. However, it should be used cautiously in patients at risk for hypermagnesemia.

D. A comparative review of literature on Ringer's lactate vs. acetate buffered solutions

While acetate-buffered solutions like PlasmaLyte have distinct compositional benefits, a thorough review of the existing literature is needed to determine their edge over Ringer's lactate. Recent literature offering insights into this ongoing debate is summarized below.

Evidence suggesting Acetate buffered solutions/PlasmaLyte is superior

- Curran et al. (2021): This systematic review with a meta-analysis of 24 trials noted that PlasmaLyte led to lower serum chloride and lactate levels and a higher base excess compared to Ringer's lactate, although the evidence is of low certainty [128].
- Ellekjaer et al. (2022): Another systematic review with a meta-analysis of five RCTs involving 390 patients found very limited, low-quality evidence supporting the use of acetate over lactate-buffered solutions in hospitalized patients for all-cause mortality [129].
- Priyanka et al. (2023): A study involving 80 children indicated a preference for PlasmaLyte over RL during perioperative fluid therapy for abdominal surgeries due to enhanced acid-base, serum electrolytes, and blood lactate profiles [130].
- Abdellatif et al. (2023): In a study with 80 children undergoing cardiac surgery, PlasmaLyte showed better lactate and calcium levels than Ringer's lactate when used as a priming solution [131].
- The inclusion of PlasmaLyte as a balanced crystalloid in recent major saline vs. balanced crystalloid trials such as SPLIT (2015), SALT (2017), SMART (2018), SALT-ED (2018), BaSICS (2021), and PLUS (2022) emphasizes its recognition and utility as a valuable option among balanced crystalloids [69–74].

Evidence suggesting equal effectiveness of Ringer's lactate and Acetate buffered solutions

- Weinberg et al. (2018): In a trial with 50 adults, PlasmaLyte and Hartmann's solution showed no significant differences in plasma bicarbonate levels, complications, or length of ICU and hospital stays during elective cardiac surgery with CPB [132].
- Pfortmueller et al. (2019): In a study of seventy-five patients undergoing cardiac surgery, the use of RL and Ringer's acetate showed similar effects on hemodynamic stability and the progression of acid-base parameters [133].
- Rawat et al. (2020): A study of fifty adult ICU patients with metabolic acidosis revealed no significant advantage of acetate solution over RL in either the speed or extent of acidosis correction [134].
- Chaussard et al. (2020): A comparison involving twenty-eight burn patients showed similar alkalinizing effects between PlasmaLyte and Ringer's lactate during fluid resuscitation. However, using PlasmaLyte resulted in significantly lower ionized calcium levels [135].

E. Summary and clinical indications of newer balanced crystalloids

The studies comparing different lactate vs. acetate-based balanced crystalloids are limited and often involve small patient cohorts, leading to no consensus on the preference for a single balanced solution [90, 136, 137]. Amongst balanced solutions, Ringer's lactate is the most preferred fluid as it is inexpensive, readily available, and its composition is favorable and more physiological. In contrast, an acetate-buffered crystalloid solution like PlasmaLyte is known for its distinct compositional advantages and is an excellent choice in specific scenarios where RL is relatively contraindicated [47]. However, it is essential to note that this preference has not yet escalated to the level of a strong recommendation. The trend to use newer balanced solutions like PlasmaLyte is growing, especially among critically ill patients with multiple organ failure and shock; however, their higher cost can be a limiting factor. The common conditions where the use of PlasmaLyte is suggested are outlined below:

- Diabetic ketoacidosis: The use of dextrose-free PlasmaLyte reduces the risk of hyperchloremic metabolic acidosis, corrects acidosis by providing bicarbonate, and offers benefits like early and faster acidosis resolution, and reduces ICU and hospital stays leading to decreased total cost [62, 138, 139].
- Perioperative fluid therapy: The use of PlasmaLyte may result in improved acid-base status, serum electrolytes, and blood lactate profiles [130]. It may be useful in major open GI and liver surgeries, including liver transplantation and complex cardiac surgeries [42, 140].In postoperative patients, using PlasmaLyte for fluid replacement on the day of major surgery has been linked to lower mortality than normal saline [66].
- Critically ill patients: PlasmaLyte is likely the optimal choice for fluid resuscitation in most critically ill, trauma patients, except those with traumatic brain injury [141–143].
- Priming the CPB circuit: Using PlasmaLyte for priming in cardiopulmonary bypass can be associated with reduced metabolic acidosis and improved calcium levels [131, 144].
- Deceased donor kidney transplantation: Using PlasmaLyte may reduce the incidence of delayed graft function in deceased donor kidney transplantation in adults [145] and decrease the risk of acute electrolyte disturbances in children [146]. Based on the findings of the ‘BEST-Fluids’ trial, PlasmaLyte should be preferred over normal saline as the fluid of choice in deceased donor kidney transplantation [145].

COLLOIDS: SECOND-LINE THERAPY FOR SELECTIVE USE

Colloids are potent resuscitation agents that rapidly improve hemodynamics with small volumes for longer periods. However, they are recommended for fluid resuscitation in only a select few patients and not as a routine practice. Commercially available colloids include natural colloids, such as albumin, and synthetic colloids, such as hydroxyethyl starch, dextran, and gelatin. Among these colloids, judicious use of albumin in selected patients is recommended, but synthetic colloids like hydroxyethyl starch, dextran, and gelatin are usually avoided or discouraged. The rationale for limited use or recommendation against the use of various colloids is summarized below, considering the literature on their benefits, disadvantages, and adverse effects.

A. The rationale for using colloids in resuscitation

- Greater volume expansion: As colloid solutions remain in the vascular space, plasma volume expansion is greater with colloids as compared to crystalloids [147, 148]. As the volume of colloids required to correct hypovolemic shock is less [149, 150], colloids prevent complications associated with the large volume of crystalloids, such as hyperchloremic acidosis, dilutional coagulopathy, and tissue edema. Accumulation of crystalloids in tissues, including lungs and incision sites, can cause weight gain, anasarca, and delayed tissue healing [151, 152].

- Faster volume expansion: Colloids are statistically more effective than crystalloids in reaching resuscitative hemodynamic endpoints [153]. The benefit of speedier achievement of hemodynamic goals with colloids compared to crystalloids is less organ damage and a decreased incidence of organ failure [148].
- More prolonged volume expansion: Because of longer intravascular half-life, colloids remain in circulation for a longer period, resulting in lesser volume requirement and better hemodynamic stability compared to crystalloids [154–156].

Review of literature

Theoretical advantages of larger and rapid intravascular volume expansion with colloids are not translated to improvement in safety and long-term outcomes in several large studies and randomized controlled trials. Summaries of significant trials, systematic reviews, meta-analyses, and guidelines comparing crystalloids with colloids are provided below.

1. Albumin trials

- Cochrane Injuries Group Albumin Reviewers (BMJ 1998): Administration of albumin for fluid resuscitation in critically ill patients may increase mortality [157].
- SAFE Study (Finfer et al. NEJM 2004): In ICU, using 4% albumin or saline for fluid resuscitation results in similar outcomes at 28 days [158].
- Cochrane Database Syst Rev (Roberts et al 2011): The review of 38 trials involving patients with hypovolemia concluded that there is no evidence suggesting that albumin decreases mortality among critically ill patients with burns and hypoalbuminemia. [159].
- Meta-analysis of five RCTs (Xu et al 2014): In this meta-analysis involving 3,658 patients with severe sepsis, those resuscitated with albumin, compared to crystalloid and saline, demonstrated a trend toward reduced 90-day mortality [160].
- Systematic review and meta-analysis (Patel et al 2014): In a study of 16 primary clinical trials including 4190 critically ill adults with sepsis, compared to crystalloids, albumin did not reduce all-cause mortality [161].
- ALBIOS Trial (Caironi et al. NEJM 2014): Comparing 20% albumin to crystalloid in 1800 septic patient resuscitation. No differences in mortality at 28 or 90 days [162].

2. Hydroxyethyl starch trials

- 6S Trial (Perner et al. NEJM 2012): Increased incidence of renal replacement therapy after HES and significantly higher 90-day mortality [163].
- CHEST Trial (Myburgh et al. NEJM 2012): Increased incidence of renal replacement therapy after HES [164].
- Cochrane Database Syst Rev 2013: The review highlighted an overall increased risk of AKI and RRT in individuals treated with HES, indicating the detrimental effects of HES on kidney function compared to alternative fluids [165].
- Recommendation of European Medicines Agency (PRCA 2013): HES should be used at the lowest effective dose for

the shortest period. HES should not be used for more than 24 hours and monitor patients' kidney function for 90 days. HES should no longer be used in patients with sepsis, burns, or critically ill patients. HES should only be used to treat hypovolaemia caused by acute blood loss when crystalloids alone are insufficient [166].

- Recommendation of European Medicines Agency (PRCA July 2018): Because of potential adverse effects, HES should be used with additional measures of protection in selected patients with acute blood loss, where for resuscitation, 'crystalloids' alone are not sufficient. HES should be used at the lowest effective dose for the shortest duration (dose less than 30 mL/kg and maximum duration <24 hours) for the initial phase of volume resuscitation [167].
- Recommendation of European Medicines Agency (July 2022): The PRAC noted the persistent use of HES solutions in contraindicated populations, increasing the risk of severe harm and mortality. Given that the associated risks outweigh the benefits, they suspended the marketing of HES and recommended opting for safer therapeutic alternatives in line with clinical guidelines [168].

3. Colloids vs. crystalloids: Trials, reviews and guidelines

- CRISTAL Trial (Annane et al. JAMA 2013): No significant difference in 28-day mortality but lower 90-day mortality in patients receiving colloids [150].
- Cochrane Database Review of 78 RCTs (2013): Colloids are not associated with an improvement in survival and are much more expensive than crystalloids. Because of the lack of survival benefits and higher costs, the routine use of colloids in clinical practice cannot be justified [169].
- Cochrane Database Review (2018): Using colloids versus crystalloids probably makes little or no difference to mortality. Starches probably slightly increase the need for blood transfusion and RRT. With the use of albumin or FFP, there is little or no difference in the need for renal replacement therapy [170].
- A systematic review and meta-analysis (Martin et al. 2019): A recent meta-analysis of 55 randomized clinical trials by Martin and Bassett concluded that crystalloids were less effective than colloids in stabilizing resuscitation endpoints in patients with a critical illness (e.g., shock, trauma, and sepsis) [153].
- Surviving sepsis campaign guidelines (Evans et al. Crit Care Med 2021): The guidelines advise using crystalloids for both initial resuscitation and ongoing intravascular volume replenishment in adult patients with sepsis and septic shock [4].
- European Society of Intensive Care Medicine (ESICM) clinical practice guideline (Arabi et al. Intensive Care Med. 2024): The recent ESICM guidelines, in general, prefer the use of crystalloids over colloids for volume expansion during resuscitation, particularly for hypovolemia not caused by bleeding [56].

B. Colloids: Current recommendations

Based on the physiological basis, literature discussed above, and other recent reviews, various colloids' current roles, advantages, and disadvantages in fluid resuscitation are summarized below.

1. Colloids are potent but not safe or preferred over crystalloids

- Crystalloids and colloids are both effective, but evidence of comparative superiority and significant benefits of colloids are lacking; therefore, current trends and recommendations including the recent Surviving Sepsis Campaign guideline (2021) and the European Society of Intensive Care Medicine fluid therapy guideline (2024), favor crystalloids over colloids for the resuscitation of nonseptic and septic patients [56, 85, 86, 97, 103, 170–172], and no indications currently exist for the routine use of colloids over crystalloids [156].
- The potential benefit of colloids to provide better hemodynamic stability is due to their effectiveness in achieving greater, rapid, and prolonged intravascular volume expansion [173].
- During resuscitation, colloids are usually used along with crystalloids when patients are likely to require a large volume of crystalloids to expand the intravascular volume [174]. Adding colloids can achieve hemodynamic stability with a smaller fluid volume, thereby reducing the risk of positive fluid balance and the associated complications, such as fatal pulmonary edema and systemic organ dysfunction that can arise from administering larger volumes of crystalloids [153].
- Colloid solutions other than albumin (e.g., Hydroxyethyl starch dextran, gelatin) are not used routinely because of lack of benefits, safety, and potential adverse effects. Several studies have demonstrated increased risks, including tubular necrosis and acute kidney injury (AKI), associated with synthetic colloid treatment [175].

2. Albumin: Safe, potent but costly option, use selectively

- Albumin is not recommended as the first-line fluid for resuscitation in both nonseptic and septic patients; instead, it should be considered a second-line option for fluid resuscitation, along with crystalloids [4, 56, 176], and in patients with cirrhosis [56]. Albumin is indicated as an adjunct to crystalloids when a patient is unresponsive to crystalloids, requires substantial amounts of crystalloids to achieve hemodynamic endpoints, or cannot tolerate large-volume crystalloid resuscitation [4, 90, 153, 177]. Albumin helps to reduce the total infused volume of crystalloids for hemodynamic stability [4, 136, 178]. IV human albumin solution is more effective for resuscitation when patients have hypoalbuminemia [178]. In septic patients, early administration of the combination of albumin (particularly 20% albumin) with balanced crystalloids within the first 24 hours of treatment decreases mortality [95, 179–181]. The use of albumin is recommended in treatment of spontaneous bacterial peritonitis, hepatorenal syndrome, large-volume paracentesis (>5 L) [176], and in patients with cirrhosis [56].
- The 30 to 100 times higher cost of albumin compared to crystalloids, along with occasional supply shortages, serves as a significant limiting factor for its use [156, 182–185].
- Avoid albumin for resuscitation in patients with severe traumatic brain injury (TBI) [54–56, 95, 186–188]. The most likely mechanism of increased mortality in patients with severe TBI is the increased intracranial pressure associated with using albumin for resuscitation. 4%

albumin is hypotonic (260 mOsmol/kg) and therefore increases brain edema [120].

3. Hydroxyethyl starch is harmful; avoid it

- Hydroxyethyl starch (HES) was once the most commonly used colloid, but due to its adverse effects, current recommendations are against its use [189]. HES is currently indicated as an adjuvant therapy for treating hypovolemia induced by acute blood loss when crystalloids alone are insufficient [190].
- HES is associated with several adverse effects including an increased risk of acute kidney injury, a higher need for renal replacement therapy, excessive postoperative bleeding, an increased need for blood transfusions, and a higher mortality rate [163].
- Strict limitations and cautious use of HES: Both the US Food and Drug Administration (FDA) [191] and the European Medicines Agency (EMA) have raised concerns about the safety of HES due to its significant harmful effects. Responding to these concerns, the EMA issued guidelines in 2013 restricting the use of HES, and these guidelines were further tightened in July 2018 [167]. According to the revised guidelines, HES should only be administered during the initial phase of fluid resuscitation, and its dosage should not exceed 30 mL/kg. Additionally, the treatment duration should be as short as possible, not extending beyond 24 hours, and it is mandatory to monitor the patient's kidney function for at least 90 days following the administration of HES [167].
- Advise against using HES: Despite implementing risk minimization measures in 2018, the use of HES persisted in populations where it posed significant health risks, including an increased mortality rate. Owing to non-compliance with product guidelines and its misuse beyond approved recommendations, the EMA suspended the use of HES on 24 June 2022 [192].

4. Dextrans and gelatins are not recommended

- Gelatin use is associated with an increased risk of anaphylaxis, AKI, bleeding, and mortality [173, 193–195]. Given that the side effects outweigh the potential benefits [82], the Surviving Sepsis Campaign Guidelines (2021) advise against using gelatin for acute resuscitation in adults with sepsis and septic shock [4].
- Dextrans are frequently utilized in vascular surgery due to their beneficial effects, such as reducing blood viscosity and potentially enhancing microvascular circulation, particularly following grafting procedures [90]. However, their use is restricted due to associated adverse effects like antithrombotic actions [196], renal dysfunction [197], hypersensitivity reactions [198], and interference with blood grouping and cross-matching. Notably, dextrans present a higher risk of severe anaphylactic reactions compared to gelatines or starches [147].

GUIDELINES FOR BLOOD TRANSFUSION IN HYPOVOLEMIC SHOCK

In the management of hypovolemic shock resulting from massive blood loss or active bleeding, administering blood transfusions in addition to fluid replacement and hemorrhage control is essential for restoring hemodynamic stability.

Transfusion decisions should always be based on the patient's clinical state:

1. In hospitalized, hemodynamically stable adult patients, blood transfusion is necessary if the hemoglobin level drops to ≤7 gm/dL (hematocrit ≤21%) [199].
2. In patients at high risk of adverse effects, including those undergoing cardiac surgery or exhibiting evidence of myocardial or other organ ischemia, a blood transfusion is required if hemoglobin drops to ≤8 gm/dL, aiming to maintain the hemoglobin level at ≥8 gm/dL.
3. In patients with ongoing significant bleeding and hypovolemia, the need for transfusion is determined based on pulse and blood pressure, the rate of bleeding, and estimated blood loss rather than solely relying on serial hemoglobin measurements. When a large volume of blood is needed, infuse one unit of plasma, one unit of platelets, and one unit of red blood cells (1:1:1 ratio), as suggested by the massive transfusion protocol [200].
4. Avoid liberal blood transfusion; hemoglobin and hematocrit should not be raised over 10 gm/dL and 30%, respectively [201]. A higher hematocrit level is unnecessary for oxygen transport and may increase blood viscosity, leading to stasis in the already impaired capillary circulation.

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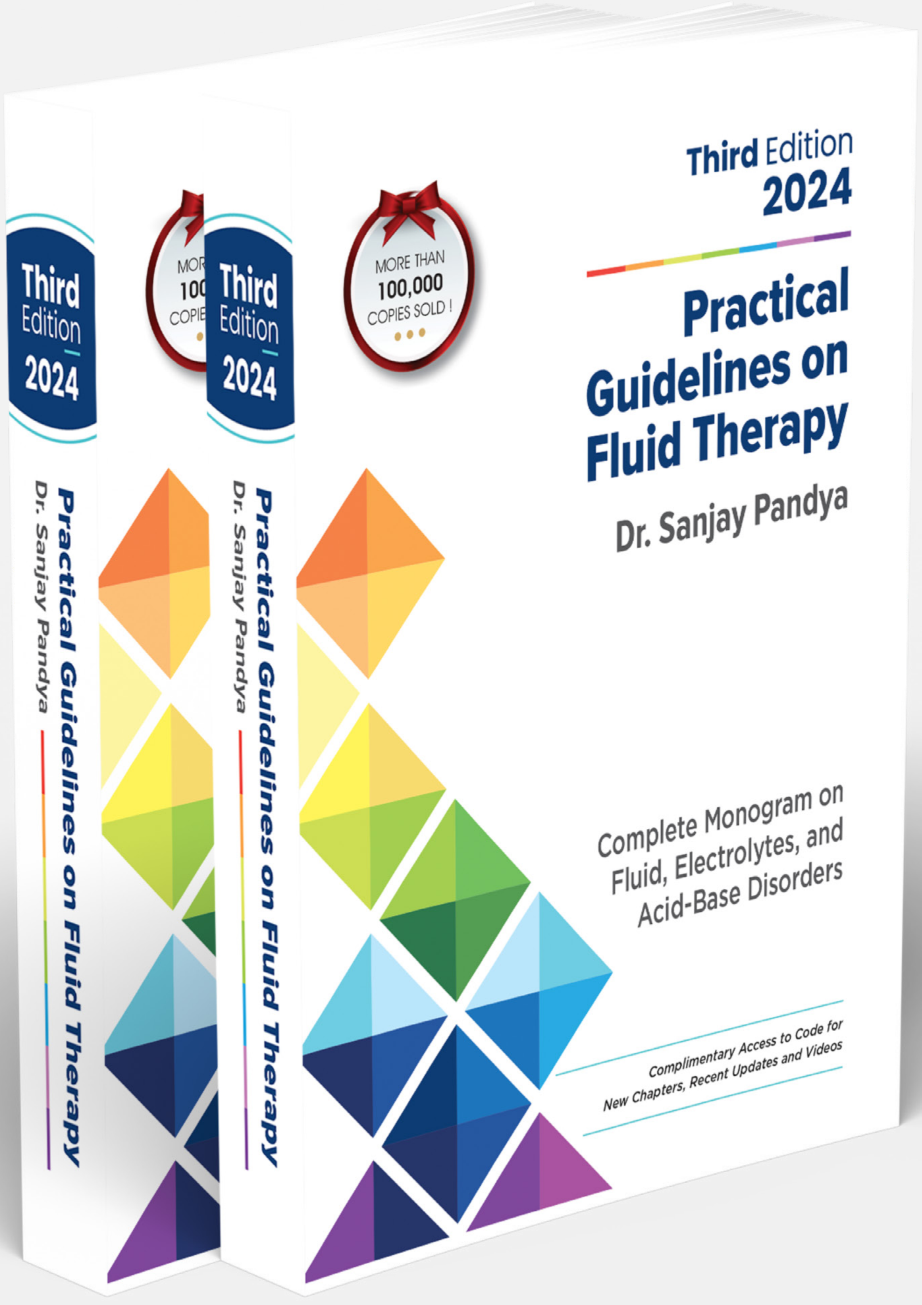
Chapter 9:

Fluid Therapy in the Elderly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Fluid Therapy in the Elderly

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Globally, Life expectancy is increasing steadily [1], so there is a need to understand the medical problems of the larger elderly population.

PHYSIOLOGICAL BASIS

To understand fluid and electrolyte disorders in the elderly, it is essential to understand physiological changes related to fluid balance in older adults. Significant relevant physiological changes are [2–5]:

- Decrease in total body water by about 10–15% due to reduced lean body mass.
- A reduction in thirst perception due to central nervous system dysfunction controlling thirst.
- Progressive reduction in renal blood flow, glomerular filtration rate and loss of renal mass.
- Impaired renal ability to concentrate urine and conserve water makes older adults prone to dehydration.
- Significant increase in atrial natriuretic peptide (ANP) activity and reduction in renin and aldosterone serum concentrations. These hormonal changes lead to an impaired ability to retain sodium, causing a greater risk of developing hyponatremia and hypovolemia.

Understanding the importance of dehydration in the elderly

It is essential to understand about dehydration in the elderly because:

- Hypovolemia is a common fluid and electrolyte disorder in the elderly [6, 7], which affects about 20% to 30% of older adults [8].
- Dehydration is the most common cause requiring hospitalization in the elderly [9, 10].
- Dehydration in the elderly is associated with a longer stay in the hospital, increased health care costs, morbidity and mortality [11–13].
- Dehydration in the elderly can cause problems like acute confusion, constipation, urinary tract infections, kidney stones, exhaustion, and pressure ulcers [14–16]. Elderly patients with dehydration can have orthostatic hypotension leading to impaired brain perfusion and dizziness, causing an

increased risk of falls and bone fractures [17].
- Timely aggressive fluid administration can improve clinical outcomes in dehydration [18].

Higher risks of dehydration in elderly patients

Reasons for the higher risk of dehydration in the elderly are:

- Reduced total body water (TBW) as a portion of body weight, so the risk of dehydration even with a loss of less volume of fluids.
- Inability to access water due to physical limitations and lack of help.
- Inadequate water intake due to decreased thirst sensation and altered awareness or mental status [5].
- With aging, renal function and ability to concentrate urine and retain fluid decline [16].
- Among older people, the habit is drinking less water than younger people [19], and the daily fluid intake of older people is below the recommended daily requirement [16].
- Common medications for the elderly such as diuretics for hypertension, increase the risk of dehydration.

DIAGNOSIS OF DEHYDRATION

In the elderly, commonly used signs and tests such as skin turgor, mouth dryness, weight change, urine color, specific gravity, or bioelectrical impedance are not useful in assessing hydration status [20, 21]. However, clinical clues like mental confusion, non-fluent speech, extremity weakness, dry mucous membranes, dry tongue, furrowed tongue, and sunken eyes provide important clues in diagnosing volume depletion in the elderly (the presence of ≥4 criteria out of 7 indicates volume depletion) [21].

Directly measured serum osmolality >300 mOsm/kg is a reliable test to diagnose dehydration in the elderly [11, 21].

NORMAL FLUID REQUIREMENT

The total fluid intake recommended for all ages by ESPEN (2022) and European Food Safety Authority (EFSA) 2010 guidelines is 2.5 L/day for men and 2.0 L/day for women [21, 22]. Out of total fluid consumed, drinking water or beverages account for 70–80%, and 20% come from consumed food [23].

Daily fluid intake is a minimum of 2.0 L/day for elderly males, and 1.6 L/day for elderly females is recommended by ESPEN and EFSA guidelines [21, 22].

PREVENTION OF DEHYDRATION

Dehydration is highly costly in older people as it causes multiple complications and is associated with morbidity and mortality. On the other hand, optimum fluid intake and prevention of dehydration offer mental, physical, and general health benefits, provides a better quality of life for older people, and save money for healthcare systems [24].

Simple steps to prevent dehydration in older persons are to ensure access to oral fluids, frequent offering of drinks, and encourage the older adult to increase their fluid intake according to their preferences throughout the day [21, 25, 26].

As dehydration is expected in the elderly, all hospitalized old adult patients should be screened carefully for early detection, preventive measures, and treatment if required, followed by frequent assessment of urine outputs and fluid balance during the hospital stay.

If diuretics are prescribed to the elderly, adjust their dose appropriately.

MANAGEMENT

The basic principles of fluid management are:

- To provide the maintenance need for fluids and to correct volume depletion, elderly patients should be given fluids, preferably orally or nasogastrically.
- Euvolemic patients who may be nothing by mouth (NPO) may need intravenous maintenance fluids. The maintenance intravenous fluid requirement is lesser in the elderly. Maintenance of intravenous fluids recommended by NICE guidelines is about 20–25 mL/kg/day in the elderly, while intravenous (IV) fluid requirement in an adult person is approximately 25–30 mL/kg/day [27].
- Elderly patients have low body weight and lesser total body water (about 45–50% of body weight in the elderly compared to 50–60% of body weight in adults), so prescribe the total volume of fluids carefully.
- Cardiac or renal impairment is common in these patients, so avoid prescribing large volumes without assessing the patient's fluid status.

The choice of IV fluids: Hypovolemic older adults who cannot drink isotonic fluids should be administered intravenously [21]. The selection of IV fluids should be individualized based on the type of fluid lost and its composition and the electrolyte and acid-base status of the patient:

- Ringer's lactate and normal saline are the most widely used IV fluids for resuscitation in hypovolemia and hypotension.
- Hypovolemia with hypernatremia due to water losses or poor intake needs supplementation of hypotonic fluid.
- In patients with diarrhea or metabolic acidosis, preferred IV fluids are balanced crystalloids like Ringer's lactate.
- Normal saline is preferred in patients with vomiting, hypovolemic hyponatremia, and metabolic alkalosis.

The volume of IV fluids administered needs careful attention and is determined based on appropriate clinical assessment, an accurate daily body weight, maintaining strict fluid intake and output chart, and measuring serum electrolyte, renal function, and serum osmolarity. Improvement in blood pressure and urine output usually suggests a response to fluid administration.

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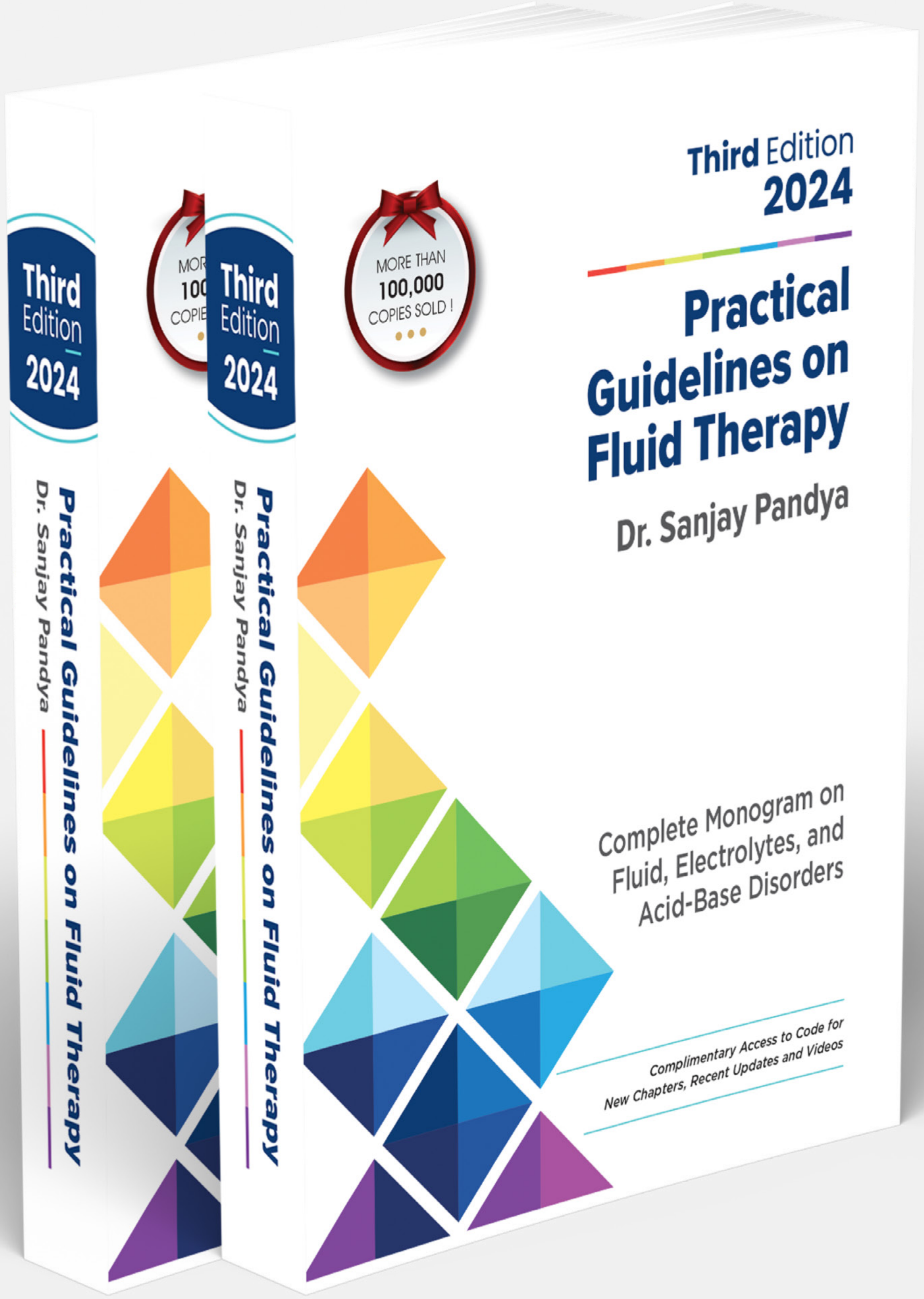
Chapter 10:

Calcium Gluconate, Calcium Chloride, and Hypertonic Dextrose Solutions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10

Calcium Gluconate, Calcium Chloride, and Hypertonic Dextrose Solutions

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Commonly used special solutions are calcium chloride, calcium gluconate, dextrose 25% and 50%, hypertonic saline, magnesium sulfate, potassium chloride, potassium phosphate, and sodium bicarbonate (Table 10.1).

Table 10.1 Composition of commonly used special solutions

Injection	Content in mEq/ml	Volume of amp (mL)	Content in mEq/amp	gm/10 ml amp
Calcium gluconate 10%	Ca^{2+} = 0.45	10	Ca^{2+} = 4.5/10 ml	1.0
Calcium chloride 10%	Ca^{2+} = 1.36	10	Ca^{2+} = 13.6/10 ml	1.0
Hypertonic (3%) saline	Na^+ = 0.5	100	Na^+ = 51/100 ml	3.0
Magnesium sulfate 50%	Mg^{2+} = 4	2.0	Mg^{2+} = 8/2 ml	1.0
Potassium chloride 15%	K^+ = 2.0	10	K^+ = 20/10 ml	1.5
Potassium phosphates	K^+ = 4.4 PH_4 = 3.0	15	K^+ = 66/15 ml PH_4 = 45/15 ml	-
7.5% $NaHCO_3$	HCO_3 = 0.9	10	HCO_3 = 9/10 ml	0.75
8.4% $NaHCO_3$	HCO_3 = 1.0	20	HCO_3 = 10/10 ml	0.84

HCO_3: Bicarbonate; Ca^{2+}: Calcium; Mg^{2+}: Magnesium; PH_4: Phosphate; K^+: Potassium; Na^+: Sodium; $NaHCO_3$: Sodium bicarbonate

Chapter 10: Calcium Gluconate, Calcium Chloride, and Hypertonic Dextrose Solutions

INJECTION CALCIUM GLUCONATE AND CALCIUM CHLORIDE

Inj. calcium gluconate and calcium chloride are two different salt forms commonly used in various emergency conditions.

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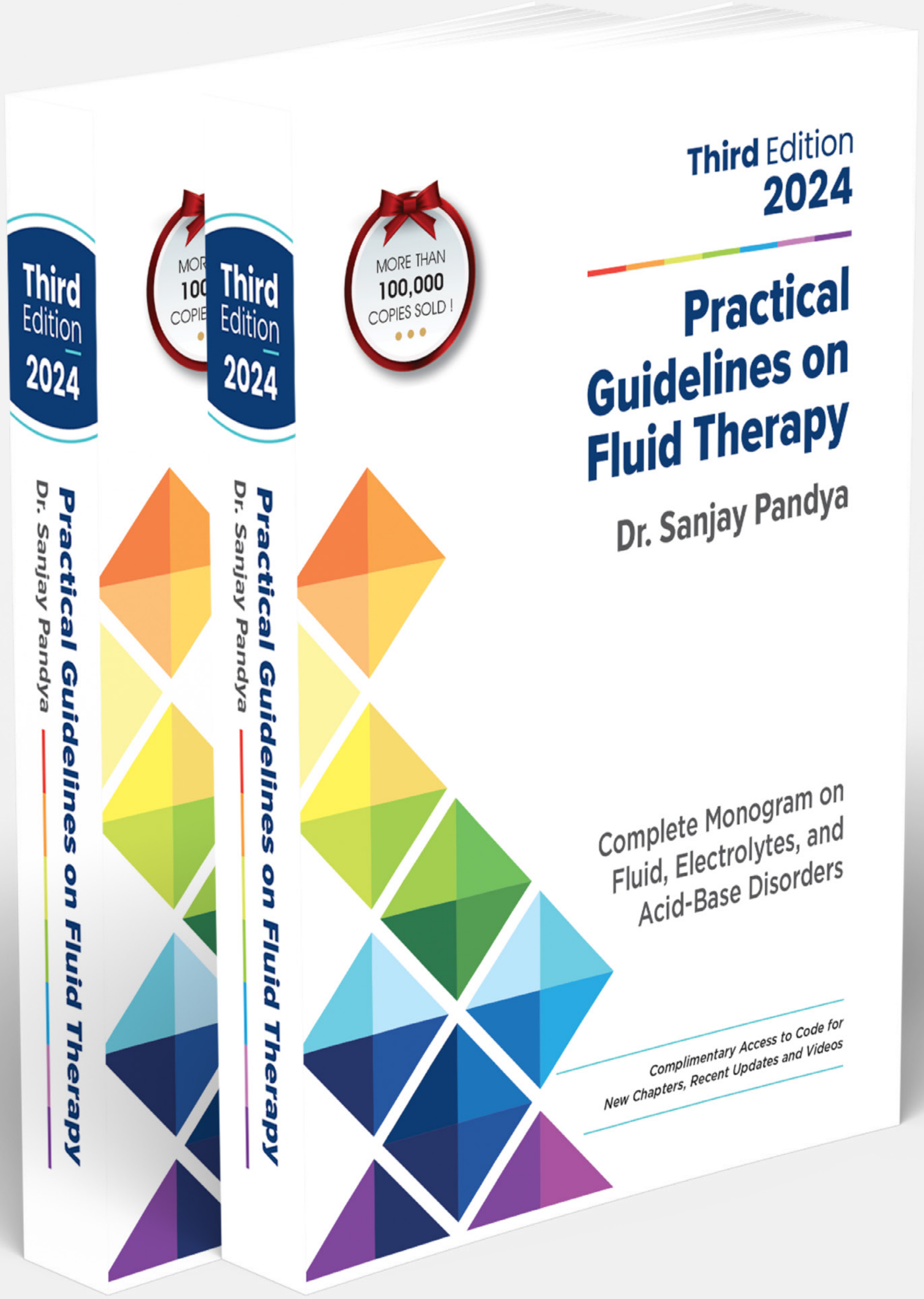
Chapter 11:

Hypertonic Saline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11

Hypertonic Saline

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  Cerebral edema and raised intracranial pressure 125
  Plasma volume expansion 126
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Hypertonic saline (HS) is a concentrated form of sodium chloride dissolved in water, and 3% and 5% hypertonic saline are commonly used solutions in clinical practice.

COMPOSITION

Inj. 3% Hypertonic Saline

Each 100 ml of contains:

Sodium	51.3 mEq
Chloride	51.3 mEq
Osmolality	1026.0 mOsm/L

100 ml of 3% NaCl contains: 3 gm of Sodium Chloride

Inj. 5% Hypertonic Saline

Each 100 ml of contains:

Sodium	85.5 mEq
Chloride	85.5 mEq
Osmolality	1710.0 mOsm/L

100 ml of 5% NaCl contains: 5 gm of Sodium Chloride

PHARMACOLOGICAL BASIS

Hypertonic saline solutions have higher sodium chloride concentration and serum osmolality as compared to normal serum values.

A. High sodium concentration promptly corrects hyponatremia

Sodium concentration of 3% and 5% hypertonic saline is 513 mEq/L and 855 mEq/L respectively compared to normal plasma concentration of 140 mEq/L. As a high sodium concentration of hypertonic saline can rapidly raise sodium and reduce cerebral edema, it is recommended in the treatment of life-threatening hyponatremia. Because of substantially higher concentrations of salt, this solution is selected to provide a large amount of sodium in a small amount of fluid (i.e., in a patient with euvolemic or hypervolemic hyponatremia who needs salt supplementation, but fluid restriction).

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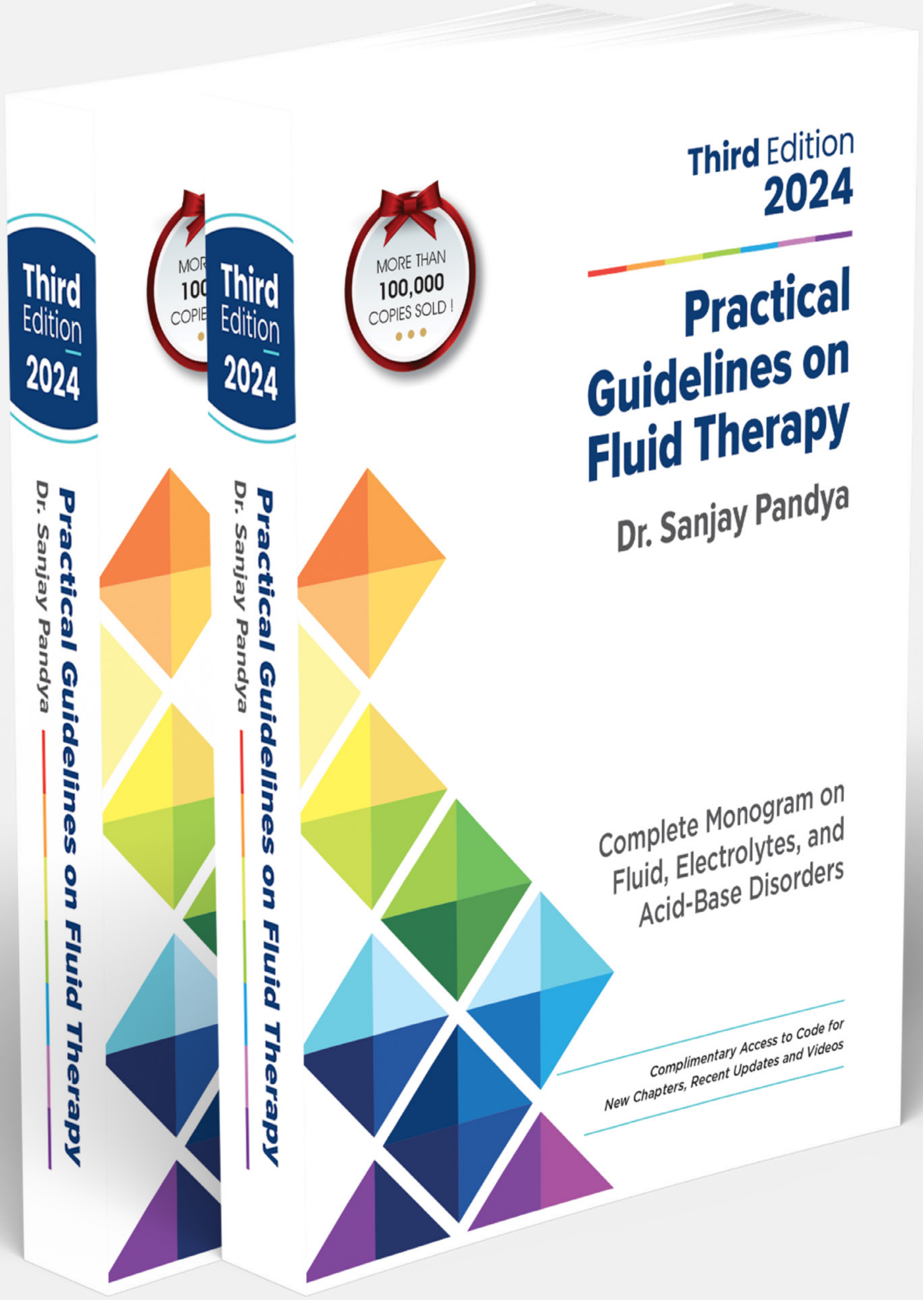
Chapter 12:

Magnesium Sulfate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Injection Magnesium sulfate ($MgSO_4$) is the most common parenterally used magnesium salt in clinical practice.

COMPOSITION

Injection Magnesium sulfate is available in different concentrations.

Inj. 50% Magnesium Sulfate

Each ml contains:
  Magnesium Sulfate USP 500 mg
  4.06 mEq or 2.03 mmol Magnesium ions
  Osmolarity 4060 mOsm/L

50% Magnesium Sulfate per ampoule: 1 gm/2 ml and 5 gm/10 ml

Inj. 20% Magnesium Sulfate

Magnesium Sulfate USP 2 gm/10 ml

Inj. 10% Magnesium Sulfate

Magnesium Sulfate USP 1 gm/10 ml

Conversion relationships: Magnesium Sulfate 1 gm = 4 mmol mg = 8 mEq mg

PHARMACOLOGICAL BASIS

Magnesium is the second most common intracellular cation. It is an essential co-factor in many biochemical reactions and plays a vital role in nerve transmission, neurochemical transmission, cardiac excitability, muscular excitability, and vasomotor tone. It also affects the regulation of calcium and potassium.

A. Preeclampsia and eclampsia

Magnesium sulfate is an effective treatment for eclampsia, but the exact mechanism of action remains unclear and is suggested to be multi-factorial (works through both vascular and neurological mechanisms) [1]. Different proposed mechanisms are:

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Chapter 13:

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Potassium Chloride and Potassium Phosphate

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Potassium chloride (KCl) and potassium phosphate are essential potassium salts used in clinical practice, with potassium chloride being the more common choice and is widely used for correcting hypokalemia. In contrast, potassium phosphate is less frequently administered and primarily used to manage or prevent hypophosphatemia.

INJECTION POTASSIUM CHLORIDE

COMPOSITION

Inj. 15% Potassium Chloride

Each ml contains:

Potassium	2 mEq
KCl	150 mg
Osmolarity	4024 mOsmol/L (calc)
pH	6.0 (4.0 to 8.0)

Available as 10 ml ampules which provides:

Potassium	20.0 mEq
KCl	1.5 mg

PHARMACOLOGICAL BASIS

Potassium is distributed chiefly intracellularly with concentrations of 140 to 150 mEq/L and is the most abundant intracellular cation. The normal range for serum potassium is 3.5–5.0 mEq/L, and its presence in extracellular fluid (ECF) is very important for the regulation of nerve conduction and contraction of muscles, particularly in the heart.

The ability of kidneys to retain potassium is incomplete (unlike sodium). Therefore, potassium loss from the body continues in patients on a potassium-free diet and even in hypokalemia. So, potassium supplementation is required in the patient on maintenance fluid therapy to avoid hypokalemia.

Moreover, in many conditions where sodium and potassium both are lost (i.e., diarrhea, vomiting, diuretic therapy, etc.), under the influence of increased aldosterone, sodium is retained, and the potassium is lost by the kidney, which causes or aggravates hypokalemia. So adequate potassium supplementation is necessary along with the administration of sodium.

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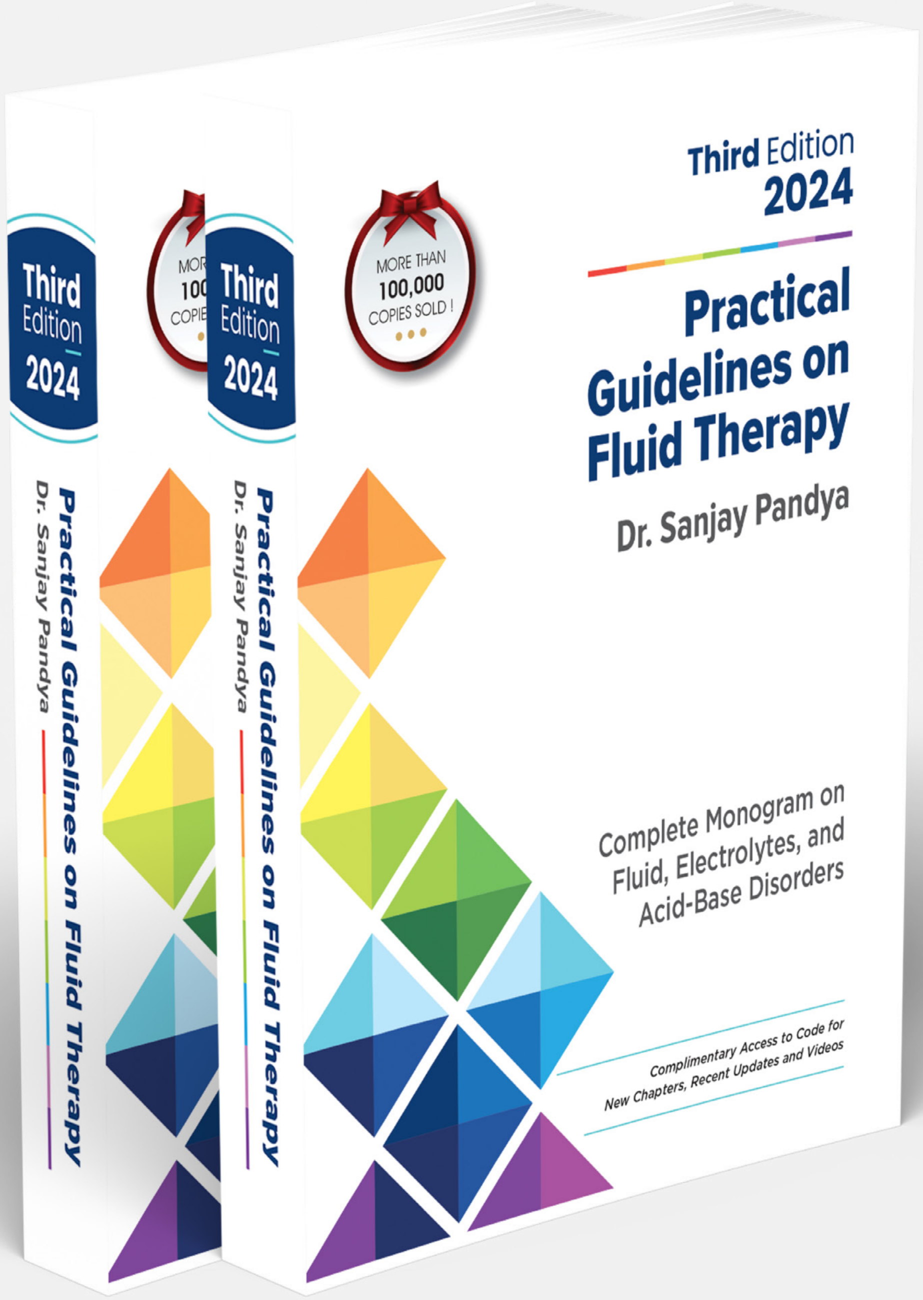
Chapter 14:

Sodium Bicarbonate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Sodium Bicarbonate ($NaHCO_3$) injection is an alkalinizing agent used to correct metabolic acidosis, manage electrolyte imbalances, and in the treatment of severe diarrhea and poisoning.

INJECTION SODIUM BICARBONATE

COMPOSITION

Inj. 8.4% Sodium Bicarbonate

Each ml contains:

Sodium	1 mEq or mmol
Bicarbonate	1 mEq or mmol
Sodium	23 mg
Bicarbonate	61 mg
$NaHCO_3$	84 mg
Osmolarity	2000 mOsmol/L

Inj. 7.5% Sodium Bicarbonate

Each ml contains:

Sodium	0.89 mEq or mmol
Bicarbonate	0.89 mEq or mmol
$NaHCO_3$	75 mg
Osmolarity	1786 mOsmol/L

Inj. 4.2% Sodium Bicarbonate

Each ml contains:

Sodium	0.5 mEq or mmol
Bicarbonate	0.5 mEq or mmol
$NaHCO_3$	42 mg
Osmolarity	1000 mOsmol/L

Table 14.1 Sodium bicarbonate solutions: different strengths and composition

Strength	4.2% $NaHCO_3$		7.5% $NaHCO_3$				8.4% $NaHCO_3$			
Volume (mL)	1.0	500	1.0	10	25	50	1.0	10	25	50
Sodium (mEq)	0.5	250	0.89	8.9	22.5	44.5	1.0	10	25	50
Bicarbonate (mEq)	0.5	250	0.89	8.9	22.5	44.5	1.0	10	25	50
Osmolality	1000 mOsm/L		1786 mOsm/L				2000 mOsm/L			

Electrolyte contents and osmolality of different strengths and volumes of solutions are summarized in Table 14.1.

PHARMACOLOGICAL BASIS

The administration of sodium bicarbonate intravenously dissociates in the body to form sodium and bicarbonate. Bicarbonate anions act as a buffer and correct metabolic acidosis by combining with hydrogen ions ($HCO_3 + H^+ = H_2CO_3^-$ carbonic acid). In addition, by increasing pH and shifting potassium intracellularly, bicarbonate corrects hyperkalemia.

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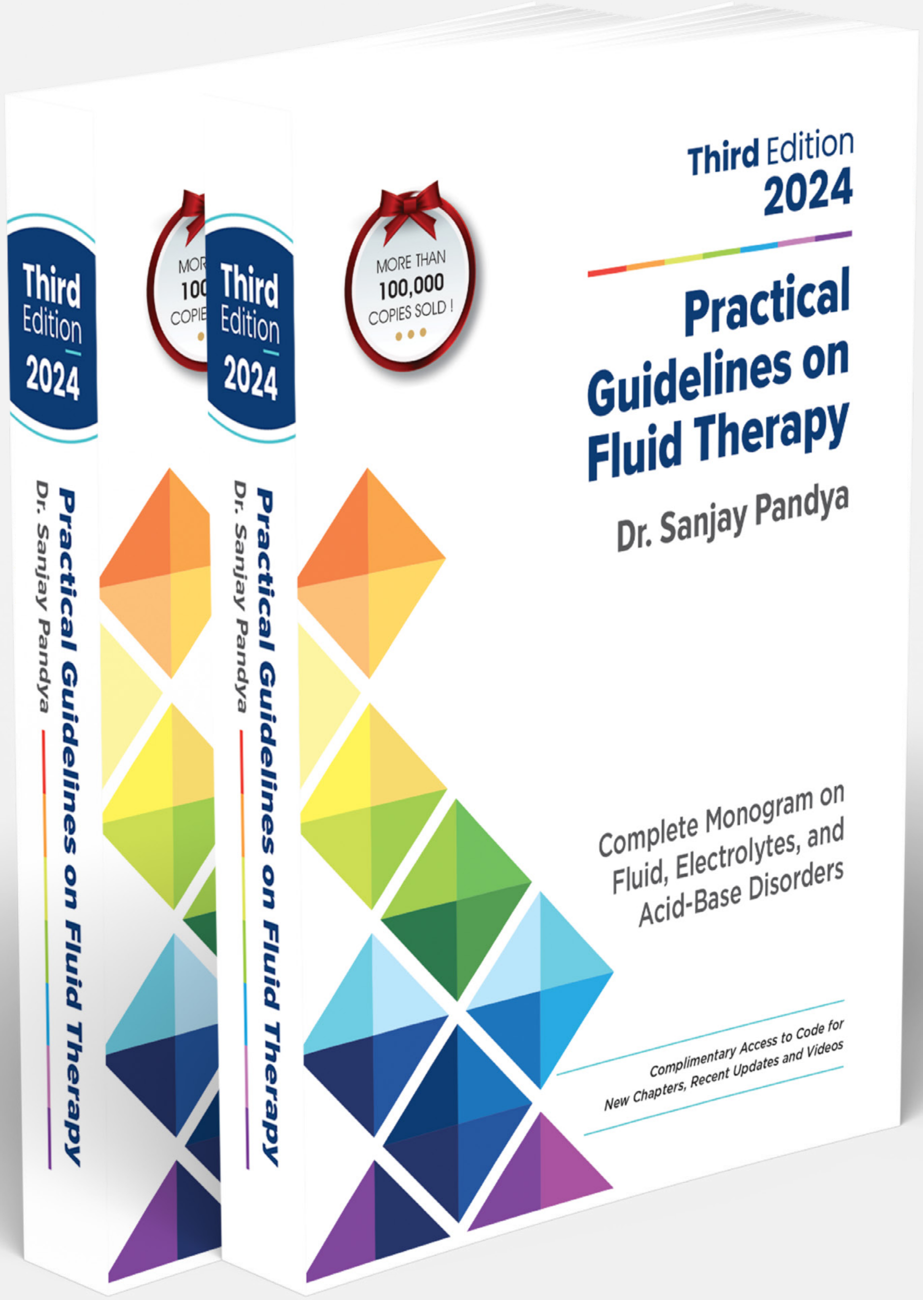
Chapter 15:

Fluid Assessment and Monitoring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15 Fluid Assessment and Monitoring

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Both inadequate or excessive fluid replacement is detrimental [1, 2], and optimum fluid replacement is beneficial and, at times, lifesaving. So, meticulous evaluation and, on its basis, planning of proper administration of intravenous (IV) fluid is critical.

The accurate assessment of body fluid volume status requires proper history, clinical examination, hemodynamic monitoring, and laboratory investigations (Table 15.1). There is no single parameter that alone can precisely assess the hydration status [3]. Therefore, after initial resuscitation, frequent reassessment and monitoring are mandatory for the appropriate subsequent fluid administration.

HISTORY

Detailed history provides valuable information about body fluid volume status and associated illnesses. Important history to be elicited are:

1. Fluid intake (volume and type of oral, nasogastric, or intravenous fluids).
2. Abnormal loss of fluid (diarrhea, vomiting, drains, high fever, and insensible losses).
3. Urine volume.
4. Symptoms of hypovolemia (increased thirst, oliguria, fatigue, weakness, or dizziness on standing).
5. Symptoms of hypervolemia (swelling, weight gain, shortness of breath with aggravation on exertion or lying down flat).
6. Coexisting illness and comorbidities (diabetes, hypertension, ischemic heart diseases, congestive heart failure, kidney failure, cirrhosis of the liver, hypoproteinemia, and malnutrition).
7. Medication (antihypertensive, diuretics, laxatives).

Table 15.1 Assessment of volume status
• History
• Clinical examination and monitoring
• Hemodynamic monitoring
• Laboratory investigations

CLINICAL EXAMINATION

It is essential to assess the volume status of the patient by proper physical examination. Based on the clinical examination, the predictability of the severity of volume depletion is poor. However, in critical patients with severe volume depletion and shock, prompt clinical assessment and proper medical history are sufficient to initiate the right treatment [4]. It is essential to know the features of hypovolemia and hypervolemia to determine the volume status.

Signs of hypovolemia: Signs of volume depletion on clinical evaluation do not always correlate with the severity of hypovolemia. However, the features, based on the degree of extracellular fluid (ECF) volume depletion, are summarized below.

Mild volume depletion (<5% reduction of ECF)

- Diminished skin turgor
- Concentrated urine
- Loss of weight

Moderate volume depletion (5 to 10% reduction of ECF), as above plus

- Oliguria (<400 ml/day)
- Orthostatic tachycardia and hypotension (fall of ≥20 mm Hg systolic blood pressure or 10 mm Hg diastolic blood pressure)

Severe volume depletion (>10% reduction of ECF), as above plus

- Hypotension
- Low pulse volume, tachycardia, tachypnea
- Cold extremities, dry tongue, sunken eyeballs
- Prolonged capillary refill time (>2 seconds), and reduced skin turgor (doughy feel)
- Abnormal mental status and confusion

Difference between dehydration and hypovolemia: Terms dehydration and hypovolemia are often confusing and used interchangeably. But dehydration and hypovolemia are fundamentally different clinical disorders with different pathogenesis, clinical presentations, biochemical features, and management [5, 6]. The term dehydration refers to pure water loss producing hypertonicity and intracellular volume contraction. While hypovolemia refers to a combined loss of salt and water, causing extracellular fluid volume deficit and contraction of the blood volume. Characteristic features of dehydration are normal blood pressure, no orthostatic hypotension, and hypernatremia. Hypovolemia is characterized by orthostatic hypotension, tachycardia, decreased skin turgor, and normal or low serum sodium.

Signs of hypervolemia: Common signs of volume overload on clinical evaluation are:

- Peripheral edema, sacral edema in bedridden, and recent weight gain.
- Distended jugular vein.
- The third spacing of intravascular fluid causing ascites and pleural fluid.
- Tachycardia, tachypnea, and orthopnea.
- On auscultation, basal crepitation in the chest and third heart sounds.

MONITORING OF FLUID BALANCE

Important steps to monitor fluid balance are:

1. Intake and output chart: Maintain a proper chart of fluid administered (enterally or parenterally) and fluid losses (urine output, abnormal losses such as diarrhea, vomiting, or losses from gastrointestinal drainage tubes, and insensible losses) to assess the fluid balance.

2. Urine flow rate: Maintaining hourly urine output is a standard practice in all hemodynamically unstable patients. Urine output reflects tissue perfusion and is an important indicator of hydration (in the absence of glycosuria, osmotic diuresis, or diuretic therapy). Fluid therapy aims to achieve a urine output of approximately 0.5 mL/kg/h or more.
3. Daily weight: The day-to-day weight chart is an accurate indicator for detecting the changes in the patient's volume status. Weight gain suggests fluid excess, while weight loss suggests fluid deficit. The inability to obtain weight is a limitation in sick patients.

HEMODYNAMIC MONITORING

Hemodynamic monitoring is a cornerstone in the management of hemodynamically unstable patients. The goal of hemodynamic monitoring is to ensure optimal tissue perfusion and to optimize the oxygenation of the tissues. Less than 50% of hemodynamically unstable critical patients are 'fluid responders', and in the rest 50% of patients, fluid administration may be harmful [7, 8], and therefore proper evaluation before administration of fluid is advisable.

Various hemodynamic monitoring techniques and parameters ranging from simple bedside examination to advanced complex methods are available (Table 15.2).

The selection of modality varies depending on the severity of the underlying disease, resources and local expertise available at each institution, predictability of the modality, and cost-effectiveness.

Table 15.2 Techniques and parameters used for hemodynamic monitoring
A. Basic and non-invasive hemodynamic monitoring techniques Non-invasive blood pressure measurement, pulse oximetry, continuous electrocardiography, ultra-sonogram, echocardiography, and X-ray chest
B. Static hemodynamic monitoring techniques Inferior vena cava assessment, central venous pressure monitoring, arterial cannulation, and pulmonary artery catheter monitoring
C. Dynamic hemodynamic monitoring **1. Provocative techniques to detect fluid responsiveness** The fluid challenge, passive leg raising, and end-expiratory occlusion test **2. Dynamic parameters to predict fluid responsiveness** Pulse pressure variation, stroke volume variation, cardiac output, and plethysmographic variability index **3. Methods and monitors used for the assessment** **a. Noninvasive cardiac output monitoring** Transthoracic echocardiography, bioimpedance or bioreactance, radial applanation tonometry, volume clamp method, ultrasound cardiac output monitoring (USCOM), and plethysmographic variability index **b. Minimally invasive cardiac output monitoring** Transesophageal echocardiography, transpulmonary thermodilution, lithium dilution, arterial pulse contour analysis, and partial CO_2 rebreathing **c. Invasive cardiac output monitoring** Pulmonary thermodilution (Intermittent bolus or continuous)

There is no single hemodynamic technique or parameter which is enough to provide sufficient information in all patients [9]. Less invasive systems are safer and therefore preferred for the initial evaluation. But invasive methods provide more predictable information and therefore are preferred in critical, unstable patients or patients with shock who do not respond to initial therapy.

Non-critical patients who are hemodynamically stable require non-invasive monitoring techniques such as continuous ECG monitoring, frequent non-invasive blood pressure measurement, and peripheral pulse oximetry to assess their oxygen saturation.

The limitations of this primary monitoring modalities is a less precise or inaccurate data, but it avoids risks of harmful invasive approaches.

On the other hand, hemodynamically unstable critical patients need more precise or highly accurate data, so they require advanced hemodynamic monitoring approaches such as arterial pulse contour analysis, transesophageal echocardiography, and transpulmonary thermodilution for continuous hemodynamic monitoring [3, 10].

Noninvasive echocardiography and ultrasonogram are currently rapidly growing and preferred modalities for the initial hemodynamic assessment of shock and perioperative evaluation instead of more invasive technologies.

Dynamic parameters such as pulse pressure variation (PPV), stroke volume variation (SVV), and cardiac output (CO) are shown to be more accurate for the assessment of the volume status. Therefore, they are preferred in predicting fluid responsiveness over static invasive measures (e.g., central venous pressure and pulmonary artery catheters) [3].

However, monitoring these dynamic parameters is not routinely recommended for patients in shock who are responding well to initial treatment. Complex, high-risk patients who do not respond to initial fluid administration need measurements of dynamic parameters to evaluate the response to fluids or inotropes [3].

LABORATORY INVESTIGATIONS

Various laboratory investigations performed considering the clinical context for the monitoring of fluid therapy are:

- Routine investigations: CBC, BUN/creatinine, transaminases, and serum electrolytes.
- Additional investigations: Serum lactate level, arterial blood gas (ABG) analysis, cardiac biomarkers, coagulation profile, and urinary electrolytes.

Serum lactate

Serum lactate estimation is the most useful and valuable laboratory parameter for monitoring critically ill patients, and the high lactate level is strongly associated with the severity of sepsis [11, 12].

Elevated lactate is multifactorial: Increased serum lactate level reflects tissue hypoxia is a misconception [13]. Increased serum lactate level is a non-specific finding which can occur due to multiple causes such as impaired tissue oxygenation, stimulation of beta-2 adrenergic receptors due to increased aerobic glycolysis, medications (adrenaline, beta-2 agonists), liver failure, thiamine deficiency, or other causes [14]. So always interpret the value of serum lactate carefully in the clinical context.

Clinical application of lactate measurement

- A tool to diagnose severe sepsis or septic shock: The measurement of lactate is useful to establish the diagnosis of severe sepsis [15] and is included in the definition of recent major sepsis guidelines such as National Quality Forum Sepsis Update [16], and third international consensus definitions for sepsis and septic shock [17, 18].

- Prognostic marker on admission: Increased lactate level in the prehospital measurement or the emergency department is associated with increased mortality even in patients with initial normal vital signs [18–22]. So early elevated lactate is useful to detect occult shock, uncover subtle organ hypoperfusion, and help to detect patients who are at higher risk for deterioration and require aggressive management.
- As a component of resuscitative algorithms: Serum lactate is included as a component of resuscitative algorithms in different guidelines (e.g., Surviving Sepsis Campaign Bundle and Surviving Sepsis Campaign International Guidelines) [23, 24].
- Lactate monitoring for a shock: In addition to clinical assessment, trends in the blood lactate levels are useful to guide resuscitation [25]. Serial serum lactate measurements during resuscitation predict mortality among septic shock patients [26, 27]. So, serum lactate level is generally remeasured every 6 hours until it becomes normal [27, 28]. Lactate-guided therapy significantly reduces hospital mortality [29–31] and has a greater mortality benefit than even early goal-directed therapy [32].
- Lactate normalization predicts a favorable prognosis: Normalization of lactate within 6 hours of initial resuscitation is the strong predictor of survival [33–36]. In a recent study, even delayed normalization of lactate (i.e., within 24 hours), independently predicts decreased mortality [37].
- Lactate clearance as a prognostic marker: Early lactate clearance reduces in-hospital mortality and strongly predicts the survivor [33, 38–41]. On the contrary, persistent hyperlactatemia increases morbidity and mortality and is a strong adverse prognostic factor [38, 42, 43].

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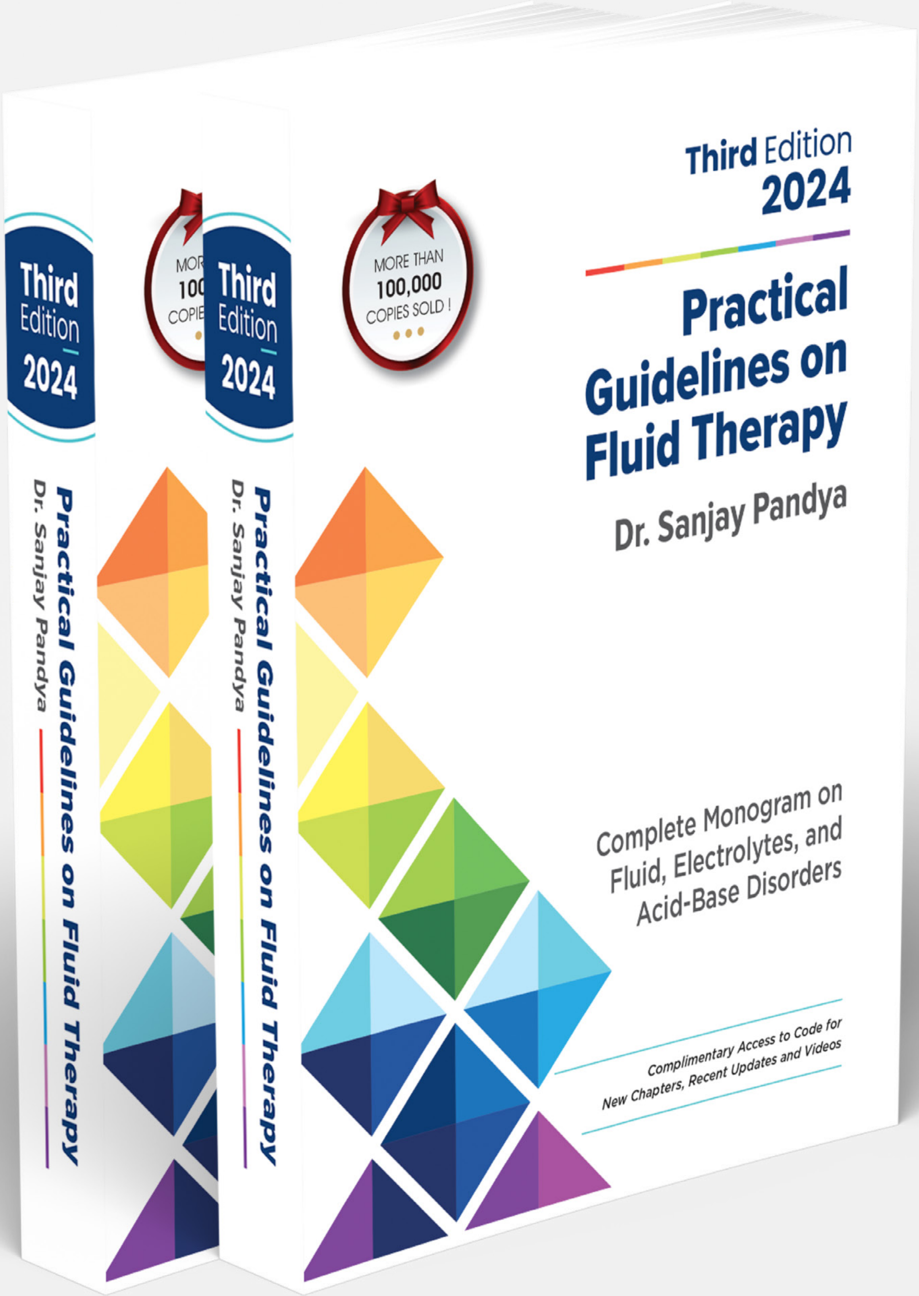
Chapter 16:

Basic and Non-Invasive Hemodynamic Monitoring Techniques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Basic and Non-Invasive Hemodynamic Monitoring Techniques

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Various basic and non-invasive methods are routinely used in clinical practice, which help to plan, administer, and monitor fluid therapy in non-critical patients. The basic and non-invasive monitoring modalities are not the standard methods for hemodynamic monitoring and lack specificity and sensitivity, but it provides valuable help in the initial assessment and management of shock. Non-invasive cardiac output monitoring is discussed in detail separately in the subsequent chapter.

NON-INVASIVE BLOOD PRESSURE MEASUREMENT

Blood pressure monitoring is a basic and easy non-invasive parameter for hemodynamic monitoring in all patients.

Non-invasive blood pressure is measured either intermittently or continuously. Intermittently blood pressure is measured by an inflatable occluding cuff using a manual sphygmomanometer or automated oscillometric devices. Continuously blood pressure is measured by newer methods such as volume clamp method or arterial applanation tonometry. Details of these methods are included in the non-invasive cardiac output monitoring part of the Chapter 19 on "Cardiac Output Monitoring."

In mild hypovolemia, compensatory mechanisms prevent a fall in blood pressure. So, normal blood pressure does not exclude hypovolemia.

Postural hypotension is a fall of at least 20 mm Hg systolic blood pressure or 10 mm Hg diastolic blood pressure within 3 minutes of standing [1]. Postural hypotension is a strong indicator of hypovolemia in the absence of other causes such as medications, autonomic neuropathy, etc.

Mean arterial pressure is a better parameter for assessing tissue perfusion than systolic blood pressure (SBP) and diastolic blood pressure (DBP). Mean arterial pressure (MAP) is the average arterial pressure in one cardiac cycle.

Formula to calculate MAP is:

MAP = [SBP + (2 × DBP)]/3

MAP of at least 60 mm Hg is necessary to maintain the adequate perfusion of vital organs. Recent Surviving Sepsis Campaign Guidelines recommended an initial MAP target of 65 mm Hg in patients with septic shock requiring vasopressors [2].

PULSE OXIMETRY

Pulse oximetry is used routinely worldwide for the rapid diagnosis of hypoxemia; It is referred to as "the fifth vital sign" [3].

Pulse oximetry is an inexpensive, non-invasive, compact, portable, and reliable technique that can continuously, rapidly, and accurately estimate arterial oxygen saturation (SpO_2) and thereby provide important information about tissue oxygenation.

Early diagnosis of hypoxemia is difficult clinically. Cyanosis is its late sign, so a pulse oximeter is used to monitor all types of patients at risk of developing hypoxemia [4]. In this easy-to-use method, the sensor probe is usually placed on fingers, toes, or ear lobes which measures two parameters, the oxygen saturation of hemoglobin in arterial blood and the pulse rate.

By using spectrophotometry, a pulse oximeter differentiates oxygenated versus non-oxygenated hemoglobin in the arterial blood and thereby measures the percentage of oxygenated hemoglobin in the blood (i.e., SpO_2). The accuracy of pulse oximeters is generally reliable when SpO_2 is in the range of 70% to 100%, but it is poor when SpO_2 values are <70% [5].

The normal value of SpO_2 in a healthy person is 96% to 100%, which correlates to the normal range of PaO_2 (i.e., 80 to 100 mm Hg). Less than 90% SpO_2 correlates to a PaO_2 of 60 mm Hg or less, which suggests significant hypoxemia, which can be dangerous [6]. When SpO_2 falls below 90%, the PaO_2 drops very rapidly. PaO_2 will be as low as 60–45 mm Hg when SpO_2 reduces from 90 to 80%, and when SpO_2 falls below 80%, it predicts life-threatening hypoxemia as the PaO_2 will be just 40 mm of Hg or even lesser [6].

Factors that can affect the accuracy of pulse oximetry are cold extremities, hypotension, poor circulation, patient movements, nail polish use, abnormal hemoglobins, and severe anemia [7].

Use of intravenous dyes like methylene blue (to treat methemoglobinemia, or to diagnose ureteral injury during surgical procedures) can result in low SpO_2 reading from a pulse oximeter but normal PaO_2 from a standard blood gas machine (known as "oxygen saturation gap") [8].

CONTINUOUS ELECTROCARDIOGRAPHY

Continuous electrocardiography monitoring is a standard practice in all unstable patients because it provides crucial information about rate, rhythm abnormality, cardiac ischemia, and abnormalities due to electrolyte abnormalities. Lead II and V1 are the most sensitive for detecting P waves and cardiac arrhythmias, while lead II, V2, and V5 are the most sensitive for detecting myocardial ischemia.

ECHOCARDIOGRAPHY

Echocardiography is a safe, simple, readily available, unique, and effective method for the initial assessment of hemodynamically unstable patients. Echocardiography is a widely used and preferred modality that helps to diagnose, monitor, manage, and follow up various clinical problems mentioned below [9–12].

- For the initial assessment of patients with hypovolemia, hemodynamic instability, and shock where it helps to differentiate various types of shock.
- To assess acute respiratory distress syndrome, right ventricular dysfunction, respiratory failure, or hypoxemia of unknown etiology.
- To diagnose pericardial effusion, cardiac tamponade, valvular obstructive or regurgitation lesions, cardiac thrombus, infective endocarditis, and pulmonary embolism.
- To assess the fluid status and by frequent evaluation guides in the tailored management of unstable patients.
- To determine the fluid responsiveness by measuring the size of the vena cava and assessing the effect of respiration, fluid challenge, and passive leg raising on it.

Respiratory variation in the vena cava, left ventricular function, right ventricular function size, and movement of the interventricular septum are the major parameters measured by echocardiography. These parameters are helpful in hemodynamic assessment and monitoring. In addition, echocardiography also provides information about cardiac output and pulmonary artery pressure, which helps to optimize patient management.

Two different echocardiography techniques used for hemodynamic monitoring are transthoracic echocardiography and transesophageal echocardiography.

A. Transthoracic echocardiography (TTE)

It is a simple tool in which an ultrasonic probe is placed on the chest or epigastrium of the subject to assess the heart and its blood vessels. For the hemodynamic assessment in patients with hypotension, TTE is performed first because it is a readily available, non-invasive, accurate, and precise technique that can be performed quickly at the bedside [13].

B. Transoesophageal echocardiography (TEE)

In TEE ultrasonic probe is placed into the esophagus and usually in a ventilated patient under sedation. As the probe is much closer to the heart in TEE, this method provides superior image quality of the heart and great vessels. Because TEE provides additional and more accurate information, it has higher diagnostic accuracy than TTE [14].

TEE is used selectively in the perioperative management of unstable surgical patients (e.g., cardiac surgical procedures, laparotomy, etc.) and in patients where TTE is not possible or provides insufficient information (i.e., chest wall injury, obese patients with poor echocardiographic window, etc.).

Although TEE provides accurate and more information than TTE, it is used in selected indications and not used routinely. Major limitations of this technique are higher cost, time-consuming method (compared to TTE), minimally invasive procedure (usually needs tracheal intubation), can be performed only on one patient at a time, and needs cleaning and disinfection after each use.

ULTRASONOGRAM

In hemodynamically unstable patients, ultrasonography may be useful in determining underlying causes for shock, such as hidden blood loss (intrathoracic intraabdominal, retroperitoneal, bladder, or extremity hematoma) or detecting the source of sepsis. Timely treatment of such potentially reversible causes of hemodynamic instability can be life-saving. Follow-up ultrasonography also helps to assess the treatment response (change in the volume of blood in pleural, pericardial or abdominal space, or improvement in the source of the infection).

LUNG ULTRASOUND

Lung ultrasound (LUS) is an increasingly used modality for assessing lung status and hemodynamic monitoring in critically unstable patients. Lung ultrasound is an easy-to-use, radiation-free, safe, less expensive, non-invasive, reliable, and reproducible bedside tool that helps in diagnosis as well as planning optimum fluid administration [15, 16].

Lung ultrasound is a powerful tool that helps to assess the fluid status and diagnose or exclude pleural effusion, pneumonia, and pneumothorax [17, 18]. In addition, bedside lung ultrasound is an effective and helpful tool for the initial evaluation of a patient with hypotension and shock, guiding fluid administration, monitoring treatment response, and detecting fluid overload early [19, 20].

Lung ultrasound is a more accurate, faster, and more convenient imaging technique than chest X-rays in emergency departments [20–22].

A. Pulmonary edema

Lung ultrasound is a useful tool that can reliably and sensitively detect pulmonary edema [16]. By assessing the volume of extravascular lung water, lung ultrasound can diagnose pulmonary edema before detecting it by any clinical signs [23]. Extravascular lung water is the amount of water in the lungs outside the pulmonary circulation, i.e., accumulated in the interstitial and alveolar spaces [24]. Therefore, lung ultrasound is recommended as a first-line test to detect pulmonary congestion, which helps in the better management of fluid administration, monitoring the response of fluid therapy, and avoiding iatrogenic pulmonary edema [25–27].

On lung ultrasound, the presence and numbers of B-lines (also termed ultrasound lung comets) reflect the volume of extravascular lung water [28, 29]. The presence of B-lines is unanimously considered a pathological finding, and B-lines are generally absent in euvolemic patients (suggests "Dry" lungs) [30, 31].

B-lines score (BLS) is the sum of all B-lines used to quantify pulmonary congestion [32]. The normal value of BLS is <5, and >15 BLS reflects moderate/severe pulmonary congestion [33]. More than three B-lines in a particular view on lung ultrasound is also a reliable clue for pulmonary edema [34]. The new appearance of B-lines is an early sign of pulmonary congestion and guides clinicians to discontinue fluid administration [35].

B. Pleural effusion, consolidations and pneumothorax

In pleural effusion, lung ultrasonography is an essential tool in diagnosing, quantifying, following the course, decision-making to drain, deciding the best puncture site for tapping, guiding the drainage insertion procedure, and diagnosing co-existing lung diseases [36–39]. In pneumonia, bedside lung ultrasound is a first-line diagnostic tool with high accuracy (94% sensitivity and 96% specificity) [40–43]. In addition, lung ultrasound is a novel tool with high accuracy and reliability in diagnosing pneumothorax (91% sensitivity and 98% specificity) [44–46].

X-RAY CHEST

Chest X-ray (CXR) is routinely used in critical, unstable patients. The major advantage of chest X-rays is immediate panoramic imaging of the thoracic structures, which provides comprehensive information and helps clinicians to suspect or exclude many pulmonary disorders [47]. However, frequent exposure of X-rays carries the risk of radiation.

In hemodynamically unstable patients, chest X-ray helps to detect fluid overload, pleural effusion, pneumonia, pneumothorax, and complications of shock such as acute respiratory distress syndrome, pulmonary embolism, and aspiration pneumonia and provides information about cardiac size and shape. In addition, a chest X-ray is frequently taken after placement of the central line to check the position of the catheter tip and to rule out iatrogenic pneumothorax.

Common chest X-ray findings of fluid overload are cardiomegaly, septal Karley B-lines, congestive vascular hilum, bilateral diffuse perihilar alveolar infiltrates in a butterfly distribution suggestive of pulmonary edema, and signs of pleural effusion. A chest X-ray is not a very sensitive or specific diagnostic test for most of these disorders, but it may be a first step in providing some important clues.

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Chapter 17:

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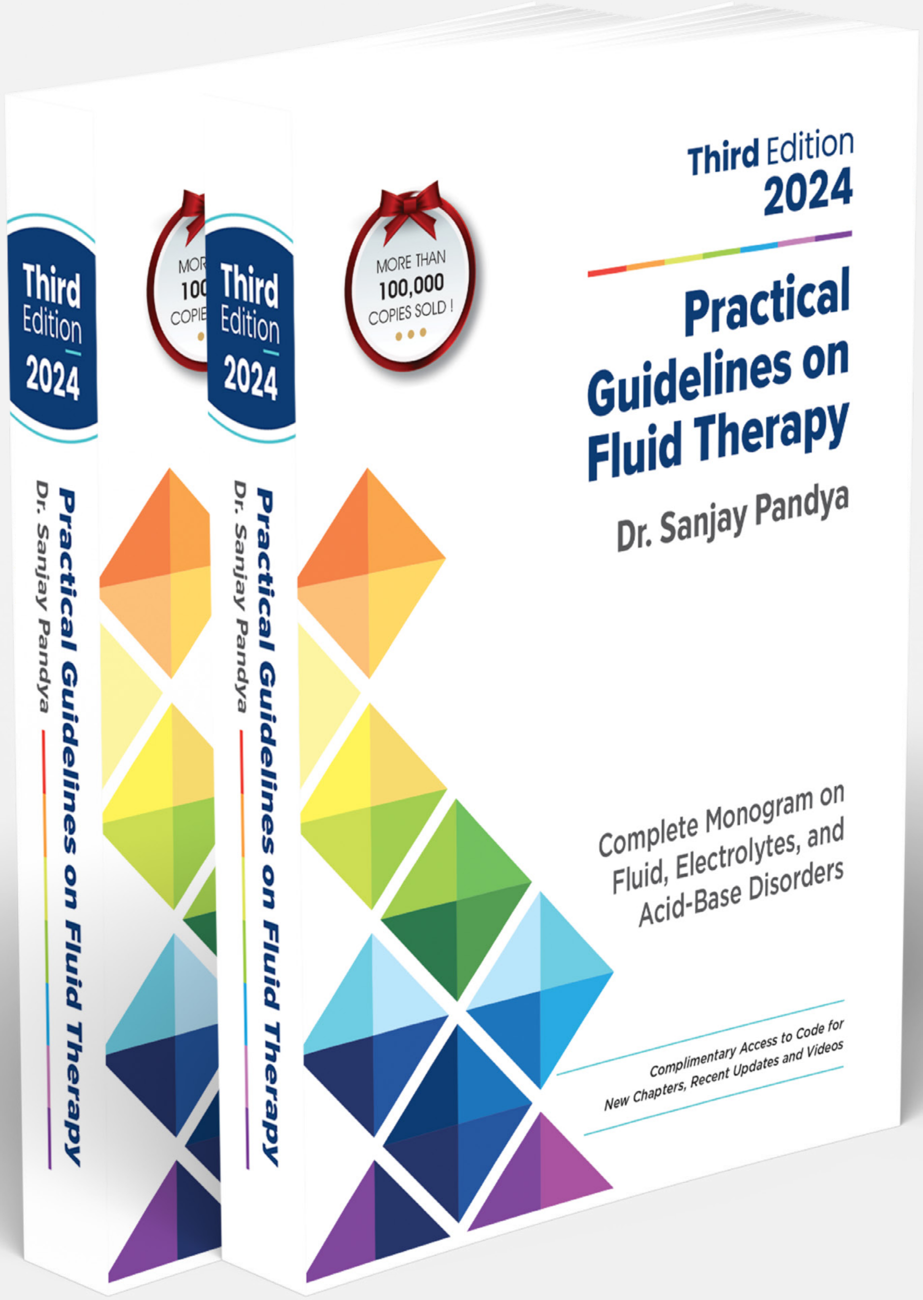
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Commonly used static hemodynamic monitoring methods are inferior vena cava assessment, central venous pressure (CVP) monitoring, arterial cannulation, and pulmonary artery catheter monitoring. Although these modalities are available more widely than compared to dynamic monitoring modalities, they lack precision and accuracy.

INFERIOR VENA CAVA ASSESSMENT

Echocardiography of the inferior vena cava (IVC) is a simple, routinely used, noninvasive tool that can rapidly measure maximal IVC diameter and respiratory variations in IVC diameter at the bedside for predicting the intravascular volume status and fluid responsiveness [1]. For the initial evaluation of shock, as compared to more invasive technologies, this modality is preferred to assess the hemodynamic status and fluid responsiveness [2, 3].

For the proper understanding clinical utility of this tool, it is discussed step by step as follows:

- Physiological variations in IVC diameter during the respiratory cycle.
- Measurement techniques.

- Maximal IVC diameter in spontaneous breathing and patients on a ventilator.
- Inferior vena cava diameter variation (IVC distensibility index (dIVC) in patients on mechanical ventilator and IVC collapsibility index (cIVC) during spontaneous breathing).

The diagnostic value of the variability of the superior vena cava is better than that of the IVC [4], but the limiting factor is a requirement of transoesophageal echocardiography for the measurement, which is minimally invasive and technically difficult [5].

A. Physiological principles

It is important to remember that amongst patients with spontaneous respiration, and in patients on positive pressure ventilation, physiological changes, values of variations of IVC parameters, and their interpretations differ markedly.

1. IVC in spontaneous respiration

In patients with spontaneous breathing, intrathoracic pressure decreases during inspiration, which increases the venous return of blood, resulting in the "collapse" of the vena cava. Inversely, intrathoracic pressure increases during expiration, which reduces the venous return of blood and thus causes the expansion of the vena cava.

IVC collapsibility index (cIVC): "Collapsibility index" is used to assess the respiratory variations in IVC diameter in patients with spontaneous respiration.

Calculation of the IVC collapsibility index: In spontaneous breathing patients, obtain the maximum IVC diameter (at the end of expiration) and minimum IVC diameter (at the end of inspiration) and calculate the index.

$$\text{IVC Collapsibility Index} = \frac{\text{Maximum IVC} - \text{Minimum IVC}}{\text{Maximum IVC}} \times 100$$

2. IVC in patients on ventilator

In patients on positive pressure ventilation (on noninvasive ventilation or intubated and on the mechanical ventilator), IVC changes with respiration are just reversed compared with spontaneous breathing. During inspiration, intrathoracic pressure increases, which pushes blood back into the IVC from the right atrium causing "Distention" of IVC. While during expiration, intrathoracic pressure decreases, and venous return increases, which causes IVC collapse.

IVC distensibility index (dIVC): "Distensibility index" is used to assess the respiratory variations in IVC diameter in patients on a ventilator.

Calculation of the IVC distensibility index and IVC diameter variability: In patients on a ventilator, obtain the maximum IVC diameter (at the end of inspiration) and minimum IVC diameter (at the end of expiration) and calculate the mean of both (mean IVC), and calculate indexes [6].

$$\text{IVC Distensibility Index} = \frac{\text{Maximum IVC} - \text{Minimum IVC}}{\text{Minimum IVC}} \times 100$$

$$\text{IVC Diameter Variability} = \frac{\text{Maximum IVC} - \text{Minimum IVC}}{\text{Mean IVC}} \times 100$$

Why is the predictive value of variations in IVC diameter better in patients on a ventilator than in spontaneous breathing patients?

In spontaneous breathing patients, respiration is highly variable between different patients, and it varies from one to another respiratory cycle, even in the same patient. Additionally, in spontaneous breathing patients, changes in intrathoracic pressure are much smaller, and therefore variation in the size of the IVC is also smaller. So, during spontaneous breathing, respiratory variations in IVC diameter are nonuniform and smaller; therefore, its predictability for fluid responsiveness is inferior [7].

While in a patient on a ventilator, controlled large tidal volume and small positive end-expiratory pressure lead to uniform changes in intrathoracic pressure during the respiration cycle. As a result, changes in vena cava diameter are also uniform (without variability from one to another cycle of ventilation), and therefore, patients on ventilators predict fluid responsiveness better than spontaneous breathing patients.

B. Measurement techniques

Two types of techniques used for the IVC measurement are:

- Transthoracic echocardiography (TTE): The diameter of the inferior vena cava can be quite easily and routinely measured by using transthoracic echocardiography using a subcostal view in a longitudinal section (measured approximately 1–2 cm caudal to the right atrium and IVC junction).
- Transesophageal echocardiography (TEE): TEE provides an accurate view of the superior vena cava (SVC) and, therefore, provides more precise data for the calculation but is used infrequently and in selected patients as this method is minimally invasive (requires intubation) with many limitations.

C. Maximal IVC diameter

Assessment of maximal IVC diameter is a static parameter that may be used to evaluate volume status and fluid responsiveness in spontaneously breathing patients [2]. In patients with shock, despite normalization of blood pressure after fluid resuscitation, inadequate dilatation of the IVC may be an important clue for insufficient circulating blood volume [8]. However, clinicians should use static IVC diameter cautiously because of its poor predictability [9]. Maximal IVC diameter is not useful in most patients, but very low or very high values may be helpful [10].

1. In spontaneous breathing

- Complete IVC collapse or end-expiratory IVC diameter less than 10 mm may suggest hypovolaemia and needs fluid administration in spontaneously breathing patients [11–14].
- IVC diameter of more than 25 mm may suggest hypervolemia in spontaneously breathing patients, and fluid administration is not appropriate [11, 15].
- In patients with marked volume overload, IVC is expanded and not collapsible [16]. However, noncollapsing large IVC diameter is not specific for volume overload, and it is essential to exclude multiple other causes [15].

2. In mechanically ventilated patients

A single static value of IVC diameter does not predict fluid status or fluid responsiveness in patients on a ventilator [6]. It is important to remember that IVC is often distended in patients on a mechanical ventilator due to increased intrathoracic pressure because of positive pressure ventilation. Therefore, a distended IVC in patients on a ventilator neither suggests volume overload nor excludes hypovolemia or fluid responsiveness.

However, an end-expiratory IVC diameter of less than 13 mm is a strong indicator of volume depletion, and an IVC diameter over 25 mm excludes fluid responsiveness in patients on a mechanical ventilator [10, 17].

Pitfalls: Between the vena cava and right atrium, there is no valve, and therefore, high right atrial pressure causes expansion of the vena cava and impairs the normal collapsibility of the vena cava. So, before diagnosing the volume status based on IVC parameters, consider other factors that can affect the IVC diameter and collapse, such as right atrial pressure, respiratory disorders affecting the degree of intrathoracic pressure change, and pressure within the abdominal cavity.

Remember that prerequisites to use IVC diameter and collapsibility to assess volume status effectively are controlled mode ventilator, tidal volume ≥8mL/kg with positive end-expiratory pressure (PEEP) ≤5 cm H_2O, intraabdominal pressure should be normal, and absence of acute cor pulmonale or severe right ventricular dysfunction [14, 15]. Fluid responsiveness is predicted poorly if tidal volumes <8 mL/kg or PEEP >5 cm H_2O [18].

D. Inferior vena cava diameter variation

In spontaneously breathing patients, the average diameter of IVC is about 18 mm, with approximately 50% collapse with inspiration [19].

Assessment of the change in diameter of the vena cava during respiration and calculation of the distensibility/collapsibility index on its basis is a widely used tool for predicting intravascular volume status and fluid responsiveness. Variations in IVC diameter in response to fluid administration is a better indicator of adequate replacement of fluid than vital signs, and static maximal IVC diameter [9].

For the assessment of fluid responsiveness, the predictive value of variations in IVC diameter is better in patients on a ventilator compared to patients on spontaneous breathing [20, 21].

The measurement of inferior vena cava diameter is routinely performed in ICUs for both patients spontaneously breathing and on a ventilator. But it is important to remember that evidence about the predictive value of this modality in the assessment of volume status and fluid responsiveness in both groups is conflicting and the subject of debate [3, 17, 22–24].

1. In mechanically ventilated patients

There are controversies regarding the effectiveness of respiratory variation in IVC diameter and distensibility index to predict fluid responsiveness in mechanically ventilated patients. There are studies, systematic reviews, and meta-analyses supporting its predictive value and use [18, 20, 21, 25–32], and data not in favor of the same [4, 10, 33–35].

The distensibility index (dIVC) is a more accurate parameter in predicting the volume status as compared to the collapsibility index (CI-IVC) and variations in IVC (ΔIVC) in patients with positive pressure supports [36].

In patients on a ventilator:

- If the distensibility index is >18% or IVC diameter variability is >12%, it may predict fluid responsiveness [25–27].
- If the distensibility index is <18%, the patient is not responsive to volume, and benefit from fluid administration is unlikely [37].

In patients on a ventilator, as compared to the measurement of IVC collapsibility, SVC collapsibility has better diagnostic accuracy in predicting fluid responsiveness [5]. The SVC collapsibility threshold of 36% can effectively differentiate between fluid responders and nonresponders patients (with a sensitivity of 90% and a specificity of 100%)

[38]. But the measurement of SVC needs semi-invasive transesophageal echocardiography, which is the limiting factor.

2. In spontaneous breathing patients

Because of conflicting evidence, use IVC diameter variation and collapsibility index cautiously to predict fluid responsiveness in spontaneously breathing patients. Evidence supports its predictive value and uses [7, 9, 20, 39–44], and there is also literature not favoring the same [21, 45–48]. Remember that optimal thresholds of these parameters in spontaneous breathing are different from those described in patients on a ventilator [39].

In spontaneous breathing patients:

- Very collapsible IVC with higher amplitude respiratory variation, i.e., collapsibility index >40%, is a moderate predictor of fluid responsiveness [7, 40–42], but lower values (<40%) do not exclude volume responsiveness [9, 19].
- Very distended IVC with a collapsibility index <15% may suggest that the patient is not fluid responsive [49].
- The absence of respiratory variation is an important clue, which suggests that the patient is not fluid responsive [26].

Besides low sensitivity and less reliability in patients with spontaneous breathing, cautious use of this modality is preferred because it is readily available, easy to perform, noninvasive, and carries high specificity [40, 43, 44].

CENTRAL VENOUS PRESSURE MONITORING

Central venous pressure is the most frequently used method to assess the hemodynamic status and guide fluid resuscitation in ICU patients [50, 51].

What is CVP?

Central venous pressure is the pressure of blood measured in the vena cava at its junction with the right atrium. CVP is a simple method that can be easily measured in any patient with a central venous line, and the most frequently chosen access is the internal jugular vein.

CVP measures mean right atrial pressure and is an indicator of chiefly right ventricular preload and, to a lesser extent, left ventricular preload.

Factors determining CVP

CVP is influenced by multiple factors such as vascular volume status, right ventricular compliance, pulmonary vascular resistance, thoracic, pericardial, and abdominal pressures, peripheral vascular tone, and posture [11, 52]. In patients on a mechanical ventilator, the value of CVP increases proportionate to positive end-expiratory pressure (roughly 5 cmH_2O increase in PEEP will cause a 2.5 cmH_2O increase in CVP) [53].

CVP measurement is unreliable in the presence of pulmonary vascular disease and hypertension, right ventricular disease, congestive heart failure, valvular heart disease, tense ascites, and high intra-abdominal pressure.

Interpretation of the value of CVP

The value of CVP should always be interpreted with clinical status.

Normal value

The normal value of CVP is 2 to 6 mmHg (when measured continuously using electronic pressure transducers) or 3 to 10 cm H_2O (measured directly using water manometers).

Low CVP

- True hypovolemia, as in blood loss, fluid loss, or fluid shift.
- Relative hypovolemia caused by peripheral vasodilatation, as in spinal anesthesia, septicemia, and anaphylactic shock.

High CVP

- Volume overload.
- Cardiac causes like congestive heart failure, cardiac tamponade, constrictive pericarditis, and tricuspid regurgitation.
- Pulmonary causes like embolism, pulmonary hypertension, tension pneumothorax, COPD, and cor pulmonale and positive pressure ventilation.

When and how to use CVP in clinical practice?

In the past, CVP monitoring was the most commonly used tool to assess volume status and to guide fluid resuscitation in critically ill patients [54]. However, in recent literature, the relationship between CVP and blood volume was poor, and CVP was unable to predict the hemodynamic response to a fluid challenge [2, 55, 56].

With recent evidence, the concept of using static marker CVP to assess intravascular volume or an indicator of fluid responsiveness is not recommended and is considered unreliable and potentially dangerous [57, 58].

However, CVP is still used in ICUs worldwide because other more accurate methods are not available easily [54].

In view of two contradictory facts (i.e., growing literature against the use and routine worldwide use in practice), different practical aspects related to indications and limitations of CVP monitoring are summarized.

Basic principles

- Normal CVP does not exclude volume depletion.
- A single value of CVP does not help in managing patients; it is always interpreted in the context of the clinical situation [57, 59].
- The "extreme" CVP values are important; it provides valuable guidance. The presence of "extreme" CVP values (CVP <6–8 mmHg and CVP >12–15 mmHg) can be of great help in predicting volume status and planning fluid administration [60–62].
- Using CVP to guide fluid administration is far from perfect, but when more accurate predictors of fluid responsiveness are not available, a reasonable CVP target is 8–12 mmHg [62, 63] during fluid administration. However, if the patient is stable, no attempt should be made to increase CVP to specific target values. Instead, the upper limit of CVP should be determined individually, considering the potential benefit/risk of further fluid administration. The goal is to keep CVP as low as possible while maintaining adequate tissue perfusion [62].

Low CVP

- A low CVP can be normal but generally suggest hypovolemia. If CVP is normal, it does not exclude hypovolaemia [64].
- In patients with low CVP values (less than 6 mmHg), an initial moderate fluid bolus is unlikely to cause harm, and most patients will respond to fluids [59–62].
- Prognostic value: In patients with circulatory shock, lower CVP and increased cardiac output may improve the prognosis and renal function, so one should try to keep lower CVP with

due caution to maintain adequate tissue perfusion [62, 65].

High CVP

- High CVP is always abnormal and has important therapeutic and prognostic values.
- An increase in CVP can occur due to increased total vascular volume, decreased cardiac function, or both.
- Patients with high CVP values (greater than 15 mmHg) do not respond to fluid administration, and therefore it is prudent to avoid the administration of fluids when the CVP is markedly elevated [61, 62].
- The upper threshold of CVP can alert the clinician to stop fluid therapy, and a positive trend reaching high values (CVP >8 mmHg) may warn the clinician that fluid replacement is no more needed [64]. So, the use of high CVP as a safety end-point and as a stopping rule for fluid administration can minimize the risk of volume overload [66].
- Prognostic value: Elevated CVP (>10 mmHg) is associated with an increased risk of mortality, a higher incidence of acute kidney injury (AKI), and poor outcomes (i.e., death) in critical ICU patients [65, 67–71]. A high CVP causes an increase in renal venous pressure leading to increased renal venous congestion, and reduces renal perfusion pressure with AKI as a result [72]. Similarly, elevated venous pressure may impair the venous return and disturb microcirculatory blood flow, which may harm the functions of different organs, leading to poor outcomes and even high mortality [58, 68].

Conclusion: Except for the extreme values, CVP may provide inaccurate estimations of volume status and does not predict volume responsiveness. When more accurate methods to estimate a patient's fluid volume status are unavailable, clinicians should understand the limitations, dangers, and benefits of CVP and use it judicially and selectively rather than abandon it altogether.

ARTERIAL CANNULATION

Arterial cannulation is a frequently performed and preferred procedure for the hemodynamic monitoring of critically ill and high-risk surgical patients [64].

Use

Arterial catheterization is useful for:

1. **Continuous monitoring of arterial blood pressure:** Arterial catheterization is a low-risk method which provides reliable information about blood pressure in unstable patients. This beside technique continuously and accurately measures beat-to-beat (as well as moment-to-moment) blood pressure and therefore recognizes the changes in blood pressure promptly and guides clinicians for quicker therapeutic interventions.
2. **Frequent blood sampling:** Arterial catheterization helps in repeated blood sampling for laboratory testing or arterial blood gas analysis.
3. **To predict fluid responsiveness:** An arterial catheter allows the analysis of arterial pressure waveforms. Analysis of respiration variations in the arterial waveform can determine fluid status and fluid responsiveness by calculating indices such as pulse pressure variation (PPV) and stroke volume variation (SVV). In addition, variations in the arterial waveform in response to fluid challenges or

passive leg raising are reliable indices for assessing fluid responsiveness.

4. **Diagnostic or therapeutic interventions:** Arterial catheterization is used for various diagnostic and therapeutic coronary procedures such as vascular stenting or embolization and intra-aortic balloon pump (IABP).

Technique

Arterial cannulation is a relatively safe procedure in which a simple cannula is introduced by a Seldinger technique, usually in a radial or femoral artery, after local anesthesia. Hemorrhage or hematoma at the puncture site, arterial spasm or occlusion, embolization, distal ischemia, and local and catheter-related infection are common complications of arterial cannulation. Avoid using arterial lines to administer medication, as it can lead to serious tissue damage and cause considerable morbidity [73].

Indications

Common indications of arterial cannulation for hemodynamic monitoring are:

- In ICU for monitoring of critically ill patients with circulatory shock.
- Major surgery such as cardiothoracic surgery or major abdominal surgery.
- When noninvasive blood pressure measurements are unreliable or difficult such as with severe burns or trauma.

Contraindications

Common contraindications of arterial cannulation are:

- Severe peripheral vascular diseases, arterial atherosclerosis, insufficient collateral perfusion, or absent pulse.
- Anticoagulation therapy or the presence of coagulopathy.

Radial or femoral, which artery to select for the cannulation?

The radial artery is a common choice because of easy cannulation due to its superficial position, the adequate collateral blood supply to the hand via the ulnar artery (reduces the risk of hand ischemia due to catheter induced thrombosis of radial artery), low rates of complications, easy to compress for the control of bleeding during cannulation or following its removal, and early ambulation [74–77]. Perform the modified Allen test before cannulation of the radial artery to assess the collateral circulation to the hands.

The limitations of the radial arterial cannulation approach are:

- Significantly smaller average lumen diameter (less than 3 mm) makes the trans-radial approach difficult in small-sized patients.
- Higher risk of thrombosis and nerve injury.
- Locating the radial artery via palpation may be difficult in patients with severe hypotension, morbid obesity, and weak pulse due to atherosclerosis.
- In patients with severe peripheral vasoconstriction and sicker patients on higher vasopressor doses, the value of radial arterial blood pressure is lower and may underestimate the central blood pressure [78–80].

The femoral artery is the second most common cannulation site [81], but the trend to use the femoral artery first is increasing in many patients with critical illness [80] because:

- It is easiest to cannulate and therefore provides faster access during emergencies in patients with shock. In severely hypotensive patients with nonpalpable peripheral pulses, greater ease in locating and cannulating due to its large lumen.

- There may be discrepancies between radial and femoral arterial blood pressure measurements. However, patients with severe hypotension on higher vasopressor doses and hypothermia femoral approach provide accurate blood pressure measurement [82, 83]. So, the femoral approach of arterial cannulation is beneficial in high-risk patients undergoing longer surgical interventions and helps to avoid inappropriate administration of vasopressors and/or inotropic agents [84].
- More reliable functioning and less likely to fail because of inaccuracy, blockage, or accidental removal [85].
- The radial artery is thin, not palpable, or there may be contra-indication to intra-arterial catheter placement at the wrist in certain patients [86].

The limitations of the femoral arterial cannulation approach are:

- Higher risk of arterial catheter-related infection [87, 88].
- Limits mobility significantly, and in alert patients, delays ambulation.
- Difficult to control or prevent bleeding (unlike radial artery), carries a great risk of retroperitoneal hematoma, and its diagnosis is often delayed [86].

PULMONARY ARTERY CATHETER MONITORING

The pulmonary artery catheter (PAC) is an invasive diagnostic procedure in which a catheter is inserted through a central vein into a pulmonary artery. PAC was used widely and considered the gold standard for measuring cardiac output in the past. But currently, PAC is used sparingly for the management of critically ill or perioperative patients [89].

Description

A pulmonary artery or Swan-Ganz catheter is a pliable catheter made from polyvinyl chloride material with a four lumen and a thermodilution sensor.

Two ports, including the Red port used for balloon inflation and the Yellow port, along with the thermodilution sensor, open within the pulmonary artery lumen, while the remaining two ports, the Proximal (Blue) port, and the White port (Clear lumen), open within the right atrium, as summarized in Table 17.1.

Technique

For the measurement of pulmonary artery occlusion pressure (PAOP), the pulmonary artery or Swan-Ganz flexible balloon-tipped, flow-directed catheter is introduced through a large vein and is placed with the tip in a distal pulmonary artery. PAC is an invasive multi-lumen central line placed through a large vein such as an internal jugular, subclavian, or femoral vein.

By using a flow-directed balloon flotation technique and utilizing pressure waveform and or fluoroscopy/echocardiographic guidance, PAC traverses along with venous blood into the vena cava (superior or inferior), right atrium, tricuspid valve, right ventricle, pulmonic valve and finally placed in the pulmonary artery [90]. Continuous monitoring of catheter tip pressure provides clues about the position of the tip of the catheter that guides the clinician to traverse the catheter to the pulmonary artery. In addition, the X-ray chest and wedge pressure waveform helps to confirm the location of PAC [91].

What information does PAC provide?

PAC provides important information by directly measuring cardiac pressures

Table 17.1 Sensor and lumens of pulmonary artery catheter

	Location	Description	Function
Thermodilution sensor	Within the pulmonary artery lumen	Located 4 cm from the tip, proximal to the balloon	It measures the blood temperature in the pulmonary artery and assists in calculating cardiac output using the thermodilution technique
Lumen or ports			
Red port Balloon inflation port	Within the pulmonary artery lumen	It terminates in the balloon at the tip of the catheter, located approximately 2 cm from the distal end	The red port is used solely for inflating and deflating the balloon by using a custom syringe and air
Thermistor lumen Distal port Yellow port		The distal port terminates at the tip of the 110 cm long catheter, which should be positioned in the pulmonary artery	The yellow port useful for measuring pulmonary artery pressure, mixed venous samples, and allows continuous cardiac output monitoring
Proximal lumen Blue port CVP port	Within the right atrium	Located 30 cm from the tip of the catheter and rests within the right atrium	It is utilized for measuring and monitoring CVP, right atrial pressure as well as for fluid and drug administration
White port Clear lumen		Located 31 cm from the tip of the catheter and rests within the right atrium	The white port is used for infusing fluids and drugs

(central venous pressure, right atrial and ventricular pressures, pulmonary arterial pressure, pulmonary artery occlusion pressure) and cardiac output [57, 92]. In addition, PAC also indirectly measures systemic and pulmonary vascular resistance, cardiac index, stroke volume, oxygen delivery, and mixed venous oxygen saturation (SvO_2).

1. Pulmonary artery occlusion pressure (PAOP)

Also known as pulmonary arterial wedge pressure (PAWP) or pulmonary capillary wedge pressure (PCWP), is a technique to measure pulmonary venous pressure and left atrial pressure indirectly by using PAC. In this method, the tip of a PAC is placed into a smaller, more distal pulmonary arterial branch. When the balloon at the distal tip of the PAC is inflated, it obstructs the forward blood flow in the distal branch of the pulmonary artery, and subsequently, measurements are obtained.

The pulmonary artery is in direct continuity with the left atrium and, therefore, with the left ventricle during diastole. So, PAOP, in addition to measurement of left atrial pressure, during diastole, reflects left ventricular end-diastolic pressure (LVEDP) and determines left ventricle (LV) function when mitral valve function is normal.

2. Cardiac output

PAC measures CO invasively using the thermodilution principle and was considered the gold standard method. Details about the same are covered in the invasive systems part of the Chapter 19 on "Cardiac Output Monitoring."

3. Mixed venous oxygen saturation (SvO_2)

It is a measurement of oxygen saturation from a blood sample from the pulmonary artery through a PAC. SvO_2 is the oxygen content of the blood that returns to the heart and is determined by cardiac output, hemoglobin concentration, oxygen supply (ventilatory settings, fraction of inspired oxygen, etc.), and tissue oxygen consumption [90].

Important causes of low SvO_2 are low or inadequate cardiac output, anemia, hypoxemia, or increased O_2 demand (sepsis, hyperthermia, burns, seizures, or shivering). The normal value of SvO_2 is 60–80%, and SvO_2 less than 65% is of poor prognostic value [93]. SvO_2 below 60% poses a serious risk of tissue hypoxia and needs urgent corrective measures.

Use of PAC in clinical practice. When and why?

The use of the PAC has decreased substantially and is not used routinely in most critically ill patients because:

1. PAC is a highly invasive technique with several complications. With the availability of less invasive hemodynamic monitoring techniques, the use of the PAC has declined in the last three decades [57, 94–96].
2. PAC failed to improve the outcome and survival [97–101].
3. Measurements of cardiac output by PAC are frequently inaccurate in critically ill patients [102, 103].
4. Static parameter like pulmonary artery occlusion pressure does not predict fluid volume [104, 105] or fluid responsiveness and therefore is not useful in fluid management in critically ill patients [106–108].

Indications

The unique feature of PAC monitoring is that it can directly measure the pressures in the right heart and pulmonary circulation [109]. PAC is the only device that efficiently assesses and continuously monitors the right ventricle function [110].

Currently, the use of PAC must be restricted to very few selected critically ill patients and complex clinical situations [92]. The most frequent indications are [2, 64, 111–113]:

- To differentiate the causes of various unexplained or multi-factorial shock states. PAC helps to differentiate cardiogenic and non-cardiogenic causes of severe shock.
- To evaluate right ventricular heart failure, pulmonary edema, pulmonary hypertension, or refractory shock, and helps in the planning of more precise fluid, inotropes, vasodilators, and diuretics treatment.
- Perioperatively in high-risk patients with severe pulmonary hypertension and acute right ventricular failure, PAC helps in the proper administration of fluids and vasopressors.
- To diagnose cardiac tamponade or constrictive pericarditis when clinical and echocardiographic findings are not conclusive.
- Preoperative assessment of intracardiac shunt, congenital heart disease, or right-sided valvular disease.

Complications

The common complications which may occur from the use of the PAC are cardiac arrhythmias, pulmonary artery rupture or thrombosis, pulmonary hemorrhage, balloon rupture, pneumothorax, catheter malposition or intra-cardiac knotting, tricuspid or pulmonary valve injury, right atrial thrombosis, internal jugular/subclavian vein stenosis, venous thromboembolism, electromechanical dissociation, and right-sided endocarditis and catheter-related bloodstream infection.

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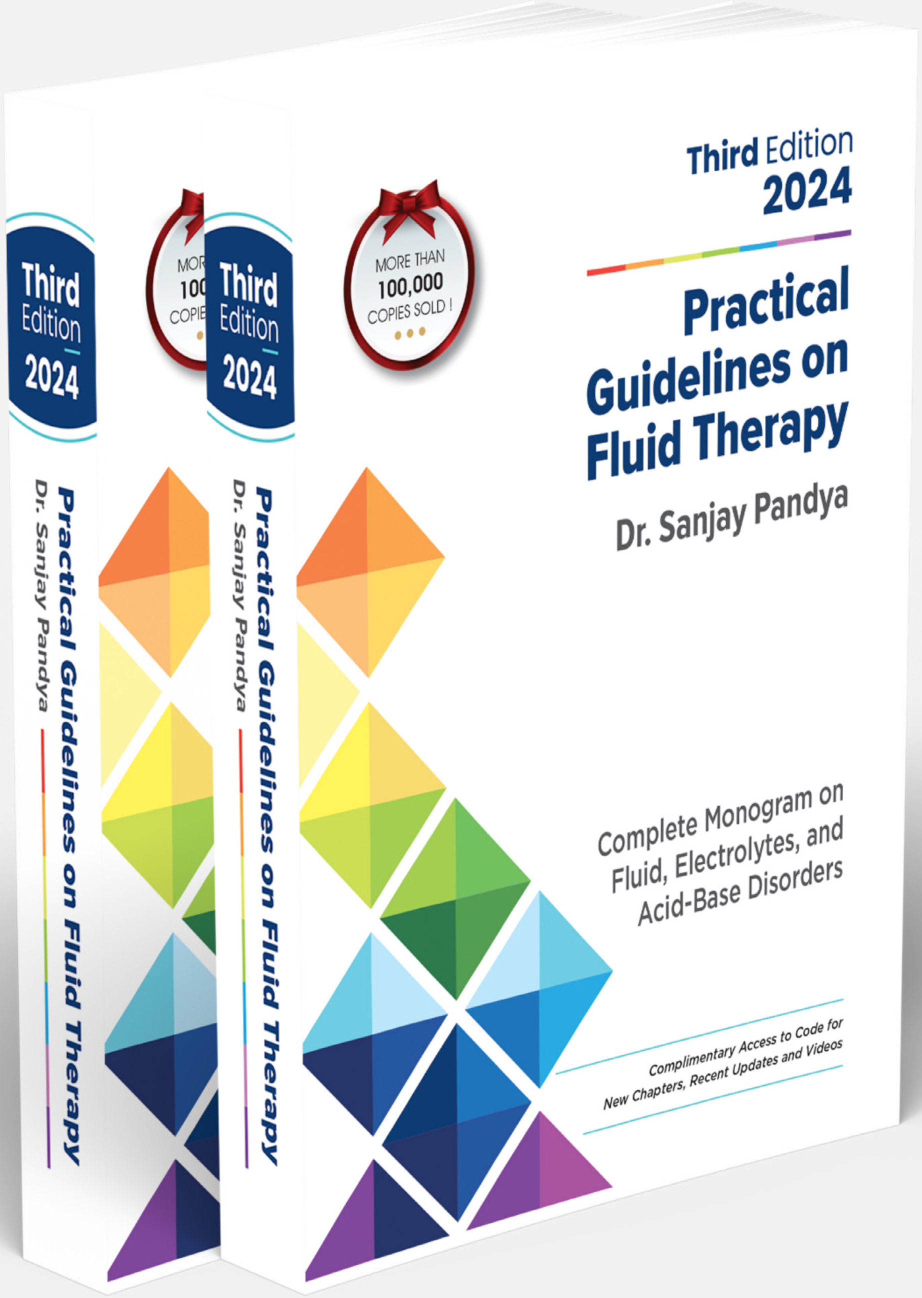
Chapter 18:

Fluid Responsiveness: Provocative Techniques and Dynamic Parameters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18

Fluid Responsiveness: Provocative Techniques and Dynamic Parameters

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Detection of fluid responsiveness is essential as it helps clinicians for the proper fluid management in critically ill patients. Various techniques are available to assess fluid responsiveness in hemodynamically unstable patients, including pulse pressure variation (PPV) and stroke volume variation (SVV), which are common dynamic measurements based on cardiopulmonary interaction derived from arterial waveform analysis.

Additionally, the plethysmographic variability index (PVI) is a simple, easily doable, noninvasive, and dynamic method that accurately predicts fluid responsiveness in mechanically ventilated patients by continuously and automatically estimating respiratory variations in the pulse oximeter waveform.

PROVOCATIVE TECHNIQUES TO DETECT FLUID RESPONSIVENESS

Why is it important to differentiate between fluid responsive from fluid nonresponsive patients by hemodynamic monitoring?

In hemodynamically unstable patients, prompt and adequate fluid administration is essential to increase blood volume, which increases venous return, cardiac output (CO), and organ perfusion. Assessment of volume responsiveness is vital in such patients because with fluid boluses, only 50% of patients with shock are benefited, and excess fluid may worsen patient outcomes [1, 2].

In which patients fluid responsiveness should be tested?

Patients do not require a test for fluid responsiveness if hypovolemia is evident on clinical examination. Avoid fluid challenge if volume overload is obvious clinically. Fluid responsiveness should be tested in hemodynamically unstable patients if fluid losses are not apparent.

Which dynamic methods are used to detect fluid responsiveness?

The use of dynamic variables is preferred over static variables to predict fluid responsiveness [3]. The fluid challenge, passive leg raising, and end-expiratory occlusion test are reliable provocative,

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Table 18.1 Summary of provocative dynamic methods to detect fluid responsiveness

Method	Fluid challenge	Passive leg raising	End-expiratory occlusion test
Nature	Non-invasive	Non-invasive	Invasive
Ventilation mode	Spontaneous	Spontaneous	Mechanical
Technique	Intravenous fluid loading	Internal volume challenge	Internal volume challenge
Effect of maneuver	Non-reversible	Reversible	Reversible
Parameters assessed	Cardiac output	Cardiac output	Cardiac output
Threshold	15% standard FC 6% mini FC	10%	5%
Methods to measure CO	Needs a very precise technique	Direct continuous measurement of CO	Direct continuous measurement of CO
	PCA, echocardiography	PCA, echocardiography, or bioreactance	PCA, echocardiography
Limitations/Exclusion criteria	Risk of volume overload	High intra-abdominal pressures, head trauma, and movement of the legs are not compatible	Non-intubated patients, 15 second respiration hold is not possible

ARDS: Acute respiratory distress syndrome; CO: Cardiac output; FC: Fluid challenge; PCA: Pulse contour analysis

dynamic methods used for the assessment of fluid status, which detects or unmasks the fluid responsive state (Table 18.1). For the assessment of fluid responsiveness, parameters such as pulse pressure variation, stroke volume variation, Plethysmograph variability index, and cardiac output are measured with commercially available various devices and monitors.

A. Fluid challenge

In the fluid challenge, a small amount of fluid is administered quickly, and the left ventricle's ability to increase stroke volume (SV) is assessed precisely [4, 5].

Fluid challenge (FC) is an effective diagnostic intervention designed to identify the "fluid responsiveness" in hemodynamic compromise patients. The fluid challenge guides clinicians to administer the optimum volume of fluid to avoid over and under-fluid resuscitation [6]. The fluid challenge is usually performed in patients with hypotension and oliguria [7].

Balanced crystalloid solutions are usually preferred for the fluid challenge because the selection of the type of fluid does not affect the proportion of fluid responders [8]. Usually, 500 mL crystalloid is administered over 20–30 minutes (or 200–250 mL is administered over 5–10 minutes) [2, 7].

How to assess the response to the fluid challenge?

The "fluid responsiveness" cannot be predicted by heart rate, blood pressure measurements, clinical signs, or static hemodynamic parameters such as central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) [9, 10].

The current recommendation is to monitor dynamic over static hemodynamic parameters after fluid challenge to predict the "fluid responsiveness" in mechanically ventilated patients [3, 10]. Even in spontaneously breathing patients, respiratory changes in dynamic parameters after fluid challenge predicts "fluid responsiveness" [11].

Cardiac output monitoring is used to assess pulse pressure variation, stroke volume, stroke volume variation, and cardiac index. Precise monitoring of these parameters is essential because the maximal effect on cardiac output occurs approximately one minute after the fluid challenge is over [12].

Which criteria define fluid responsiveness in the fluid challenge?

Usual parameters suggestive of fluid responsiveness are 10–15% increase in stroke volume [4] with a ≥15% increase in cardiac index [7]. Only fluid responsiveness patients should receive additional fluids [13].

Why is large volume fluid administration avoided for the fluid challenge?

The standard challenge with 300–500 mL of fluid is more a treatment than a test and, when repeated, carries the potential risk of volume overload. Volume overload is deleterious and probably more harmful than hypovolemia [14]. Potential harms of large volume fluid bolus are hypervolemia, pulmonary edema, bowel wall edema, endothelial glycocalyx damage, increased vascular permeability, tissue hypoxia, and organ dysfunctions [15, 16].

Positive fluid balance also increases the risk of acute kidney injury, slower recovery in acute respiratory distress syndrome, and higher mortality [17–21].

After large volume fluid bolus, clinical and physiological improvement occurs initially, but no long-term improvement, and on the contrary, causes higher mortality due to delayed cardiovascular collapse [22–24].

Why hemodynamics improvement following fluid bolus is short-lived?

Short-lived hemodynamics improvement following fluid bolus is because of rapid "Third" Spacing. In critical patients with leaky capillaries, 95% of the infused fluid shifts to interstitial space within 90 minutes, so transient benefit is lost rapidly [21, 25].

What is a mini-fluid challenge?

A mini-fluid challenge is an alternative approach that can reliably predict fluid responsiveness without a large amount of fluid infusion and the potential risk of fluid overload [26–29].

Protocols in the mini-fluid challenge includes:

- 100 ml of the crystalloid bolus is infused rapidly over one minute [26].
- A fluid bolus of 4 mL/kg of a balanced crystalloid solution is quickly infused over 5 minutes [30].

Fluid responsiveness in the mini-fluid challenge can be reliably predicted by velocity-time integral (VTI) measured by transthoracic echocardiography [29], pulse contour analysis derived from cardiac output [26], or changes in SVV [31]. As a small volume of fluid administration causes small and short-lived hemodynamic changes, response assessment should be monitored by very sensitive and precise techniques [26].

B. Passive leg raising test

The passive leg raising (PLR) test is a simple, safe, reliable non-invasive, and reproducible bedside test to evaluate fluid responsiveness in patients with spontaneous breathing, on a ventilator, low lung compliance, and even in the presence of cardiac arrhythmias [32–36]. Three metanalyses have confirmed the role of the PLR test in the assessment of fluid responsiveness [33, 37, 38].

In the PLR test, about 300 mL of blood from the lower extremities' veins is transferred into the thorax, which increases cardiac output [39]. The temporary gravitational shift of venous blood into the central circulation mimics a fluid challenge. Prediction of fluid responsiveness without administering a single drop of fluid avoids the risks of fluid overload. Rapidly reversible hemodynamic effects and no need for mechanical ventilation or sedation are the advantages of this test.

How to perform the passive leg raising test?

The basic method to perform the PLR test is [40]:

- Start the test by placing the patient 45 degrees head-up semi-recumbent (and not supine position) for 3 minutes and obtain the baseline hemodynamic values.
- The next step is to lower the patient's upper body and head to the horizontal position and passively raise legs at 45 degrees by changing the bed position (i.e., not manually) and holding in this position for one minute. Immediately assess the effects of PLR by obtaining the hemodynamic values again.
- As hemodynamic effects of the PLR test are short-term and transient, obtain the subsequent hemodynamic values fast within the first 90 seconds following leg elevation.

Assessment of the effect of the PLR test and its clinical utility

- To assess the hemodynamic effect of the PLR test, techniques which directly measure cardiac output should be used rather than methods that measure arterial pressure or pulse pressure [40]. Direct measurement of cardiac output is the more reliable hemodynamic parameter to assess the effects of the PLR test [37].
- Positive PLR test is defined as a 10% or more increase in cardiac output/stroke volume or pulse pressure, and it predicts fluid responsiveness [38, 41]. If, in response to the PLR test, an increase in cardiac output is less, it predicts a poor response to fluid administration.
- The most frequently used measurement/monitoring techniques for the direct measurement of cardiac output in the PLR test are arterial pulse contour analysis, transthoracic echocardiography, esophageal doppler, bioreactance, and contour analysis of the volume clamp-derived arterial pressure. In the PLR test, simple measurement and monitoring of systolic blood pressure by the oscillometric non-invasive method is not a sensitive or specific predictor of fluid responsiveness [42].
- During renal replacement therapy, a positive PLR test predicts subsequent hypotension even before fluid removal [43].
- As a positive PLR test predicts fluid responsiveness, a negative PLR test provides an important clinical clue to discontinue or stop fluid administration [40]. The negative PLR test helps the clinician to avoid fluid overload and guides them to select other measures like vasopressors rather than fluid administration in hemodynamically unstable patients.
- PLR test is not useful in patients with raised intra-abdominal pressure (may cause false-negative result), not feasible intraoperatively during anesthesia or in agitated patients, avoided in neurotrauma patients (may increase intracranial pressure), and in those requiring immobilization (traumatic hip or lower limb fractures)

or using compression stocking [32, 44–46].

C. End-expiratory occlusion test

The end-expiratory occlusion (EEO) test is a simple test in patients undergoing mechanical ventilation, which predicts fluid responsiveness reliably in the operating room and ICU [27, 47, 48].

In this preload responsiveness test, a ventilator is interrupted for 15 seconds at the end of expiration, and cardiac output is measured. A more than 5% increase in cardiac output predicts fluid responsiveness with a high degree of accuracy [9, 49]. The standard method used to measure cardiac output in this test is pulse contour analysis, but recent evidence supports the use of even echocardiography [48, 50, 51].

Physiological basis [52, 53]:

- In patients on positive pressure ventilation, during inspiration, intrathoracic pressure increases, which pushes blood back from the right atrium and reduces the systemic venous return.
- In patients on a ventilator, during the expiratory phase, intrathoracic pressure reduces, which allows the return of systemic venous blood. When a ventilator is stopped for 15 seconds at the end-expiration, the reduced intrathoracic pressure will persist for additional 15 seconds, permit venous return for a more extended period, and allow a larger volume of venous blood return.
- The effect of increased venous return will be like a mini self-volume fluid challenge, a transient increase in the venous blood return with a resultant increase in the left ventricular stroke volume and cardiac output.
- With the EEO test, cardiac output will increase in fluid responsive patients while no significant increase in cardiac output in non-volume responders.
- When a 15-second end-inspiratory hold is added to hold in the end-expiratory phase, the combined effect induces more substantial cardiac output changes in fluid responders, increasing the diagnostic threshold of this test to 13% and the assessment possible by echocardiography examination [50].

Reliability, even in patients with cardiac arrhythmias, acute respiratory distress syndrome, low lung compliance, and low tidal volume, are the advantages of this easy-to-use test [9, 53–55]. But this test can be performed only in patients on a ventilator who can hold respiration for 15 seconds without interruption by a spontaneous breath.

EEO test is a preferred technique to measure CO in surgical patients in the operating theatre. It can be conveniently and safely performed in sedated patients on a ventilator and with the benefit of the assessment without fluid administration (i.e., risk of volume overload). In addition, it has no technical constraints like a passive leg raising test [27, 56].

DYNAMIC PARAMETERS TO PREDICT FLUID RESPONSIVENESS

Pulse pressure variation, stroke volume variation, and plethysmographic variability index are common dynamic measurements based on cardiopulmonary interaction derived from the arterial waveform analysis, which is used to predict fluid responsiveness.

Pulse pressure variation (PPV) and stroke volume variation (SVV)

Arterial waveform derived dynamic parameters such as pulse pressure variation and stroke volume variation are accurate and excellent predictors of fluid responsiveness in mechanically ventilated patients [57–60]. Dynamic parameters PPV and SVV are superior to traditionally used static indices to predict fluid responsiveness, such as central venous pressure and pulmonary artery occlusion pressure [57, 61–64].

PPV, SVV, and cardiac output can be easily recorded and automatically calculated by many modern commercially available bedside monitors.

A. Pulse pressure variation

Pulse pressure is the difference between systolic and diastolic blood pressure, which varies with respiration. Pulse pressure variation is calculated from the maximum pulse pressure (PPmax), minimum PP (PPmin), and mean PP (PPmean) during a respiratory cycle. These values can be obtained accurately by arterial catheters, and for the calculation, the values from three or more breaths are measured and averaged.

$$\text{Pulse Pressure Variation} = 100 \times \frac{\text{PPmax} - \text{PPmin}}{\text{PPmean}}$$

Interpretation of PPV for fluid administration:

1. PPV >13% is strongly associated with volume responsiveness [57, 58].
2. If PPV is low (<9), it suggests fluid unresponsiveness, and administration of fluids should be avoided [60].
3. PPV 9–13% is a grey zone value, and a definite strategy to administer intravenous (IV) fluid cannot be made on its basis [65, 66].

PPV has a higher predictive value for fluid responsiveness compared to SVV [67, 68]. Values of PPV are reliable, provided the patient is intubated and is on a volume cycled ventilator making no spontaneous respiratory efforts, tidal value >8 mL/kg body weight, and no arrhythmias [69, 70]. However, the accuracy of PPV in patients with increased intra-abdominal pressure is questionable as there is evidence supporting [71, 72] and against [73] its reliability.

Role of PPV to guide and monitor fluid administration in clinical practice [60]:

1. Surgical patients: Its applicability is higher during major surgery because PPV improves postoperative outcomes, and in patients on mechanical ventilator accuracy of PPV is greater.
2. ICU patients: Use of PPV is lesser in ICU because in the presence of commonly encountered conditions in ICU such as cardiac arrhythmias, spontaneous breathing, ventilatory support with low tidal volume, low lung compliance (e.g., acute respiratory distress syndrome), etc., the predictive value of PPV is unreliable.
3. Interpretation in low tidal volume ventilation: In patients on low tidal volume ventilation, PPV value can be misleading as it can be low even in fluid responsiveness patients. The 'tidal volume challenge' is a simple bedside test that helps to overcome the difficulty in interpretation in such patients. In this technique, tidal volume is increased from 6 to 8 mL/kg for 1 minute, and the resultant absolute changes in PPV are measured [69, 74]. If an increase in the absolute value of PPV is 3.5% or more, it predicts fluid responsiveness with excellent accuracy [74].
4. Interpretation in grey zone values of PPV: In patients with PPV 9% and 13% and tidal volume ≥8 mL/kg, PVV is inconclusive in predicting fluid responsiveness [65]. In such patients, augmented PPV (i.e., transient increase in tidal volume from

8 mL/kg to 12 mL/kg, known as a tidal volume challenge technique) can offer excellent predictability of fluid responsiveness [75].

B. Stroke volume variation

Left ventricular stroke volume variation, like PPV, is a dynamic parameter useful in diagnosing volume deficit and is a reliable predictor of fluid responsiveness in mechanically ventilated patients. Stroke volume variation is the percentage change between the maximal and minimal stroke volumes (SV) averaged over several respiratory cycles.

$$\text{Stroke Volume Variation} = \frac{\text{SVmax} - \text{SVmin}}{\text{SVmean}}$$

SVV greater than 10% is associated with fluid responsiveness [76, 77]. The SVV is commonly measured by an arterial catheter but can also be measured by other methods such as esophageal doppler, bioimpedance, and bioreactance.

PPV and SVV are unreliable in patients with spontaneous breathing, on a mechanical ventilator with low tidal volume (<8 mL/kg), cardiac arrhythmias, right ventricular dysfunction, and low lung compliance [78–80].

C. Plethysmographic variability index

The plethysmographic variability index (PVI, Pleth variability index) is a simple, completely noninvasive, and dynamic method that accurately predicts fluid responsiveness in mechanically ventilated patients [81–83].

In this easy-to-use method, the pulse oximeter measures the light transmitted through the vascular bed of a finger and detects the dynamic change in the perfusion index during a complete respiratory cycle [84].

Continuous measurement derived from the plethysmographic waveform signals of the pulse oximetry is automatically calculated and displayed on the monitor's screen [85].

The PVI is calculated from the perfusion index (PI) variation between inspiration and expiration phases, as follows:

$$\text{PVI} = \frac{\text{PI Maximum} - \text{PI Minimumn}}{\text{PI Maximum}} \times 100\%$$

Generally, a PVI value >14% predicts preload dependence and is suggestive of fluid responsiveness [81, 86, 87].

PVI is a reasonably reliable predictor of fluid responsiveness in perioperative and critically ill patients with mechanical ventilation [88–92]. PVI guided goal-directed fluid management has been shown to improve outcomes in major surgery [93, 94]. However, in a recent meta-analysis, the reliability of PVI to predict fluid responsiveness was found to be limited, but it can play a role as a continuous bedside monitor in ICU [95].

Results of PVI are less reliable in pediatric patients with spontaneously breathing, with cardiac arrhythmias [88], probe malposition, patient motion, and in patients receiving norepinephrine (due to vasopressor induced dampened plethysmographic signals) [96, 97].

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fluid

Chapter 19:
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The accurate measurement of cardiac output (CO) is essential in all high-risk hemodynamically unstable patients.

Several devices for cardiac output measurement are available in the market, which is classified based on invasiveness (Non-invasive, minimally invasive, and invasive systems), the technology used (dilution technique, pulse contour analysis, doppler principle, applied Fick principle bioelectric properties, plethysmographic analysis, etc.), and calibration systems, as summarized (Table 19.1).

CALIBRATED VS. UNCALIBRATED DEVICES

Calibration is the process of comparing an instrument with the known standard. Subsequent adjustment of measured equipment achieves precision and accuracy and produces valid data. In calibrated monitoring devices, the bias in the continuous measurements is reduced or eliminated by calibration [1]. While in non-calibrated monitoring devices, bias is reduced by the pre-programmed correction factors in the monitoring device.

Table 19.1 Hemodynamic monitoring systems

Methods	Requirements	Calibration	Devices
1. Non-invasive systems			
Transthoracic echocardiography	Thoracic echo probe	Calibrated	US, Echo
Bioimpedance or bioreactance	Specific cutaneous electrodes	Non-calibrated	BioZ Dx ECOM NICOM (Cheetah)
Radial applanation tonometry	Pressure sensor over the radial artery	Non-calibrated	T-line
Volume clamp method	Finger pressure cuff	Non-calibrated	CNAP Clearsight/Nexfin
Ultrasound cardiac output	Transthoracic doppler probe	Non-calibrated	USCOM
Plethysmographic variability index	Specific transcutaneous probe	Non-calibrated	MASSIMO
2. Minimally invasive systems			
Transesophageal echocardiography	Esophageal probe	Calibrated	Cardio Q WAKI TO
Transpulmonary thermodilution	Thermistor-tipped arterial catheter Central venous line	Calibrated	PiCCO VolumeView EV 1000
Lithium dilution	Arterial catheter Central venous line	Calibrated	LiDCO LiDCO Plus PulseCO
Arterial pulse contour analysis	Arterial catheter	Calibrated	PiCCO Plus LiDCO Plus
		Non-calibrated	Flotrac/Vigileo LiDCO rapid PRAM/MostCare ProAQT/PulsioFlex
Partial CO_2 rebreathing	Rebreathing circuit	Non-calibrated	NiCO
3. Invasive systems			
Pulmonary thermodilution	Pulmonary artery catheter Central venous line	Calibrated	Swan-Ganz pulmonary artery catheter

Cardiac output monitoring systems are divided into two groups, calibrated and uncalibrated devices, depending on the method of calibration [1, 2]. Cardiac output monitoring systems based on non-calibrated analysis have been emerging as the preferred modality in the last few years because of their minimally invasive nature and no need for calibration, usual independence from mechanical ventilation, and ease of use in practice [3]. Uncalibrated systems are used selectively in hemodynamically stable patients requiring cardiac output monitoring for a short period, e.g., during surgery [4]. Because of more accuracy and precision, calibrated techniques are preferred over uncalibrated methods in severely shocked hemodynamic unstable patients [2].

NON-INVASIVE SYSTEMS FOR CARDIAC OUTPUT MONITORING

Non-invasive techniques commonly used for measuring cardiac output are transthoracic echocardiography, thoracic electrical bioimpedance, thoracic bioreactance, applanation tonometry, and volume clamp method.

A. Transthoracic echocardiography

Measuring and monitoring cardiac output is valuable for diagnosing and managing critically ill patients. The trend to use transthoracic echocardiography (TTE) for the prompt measurement of cardiac output is increasing because it is a readily available, reproducible, and non-invasive, bedside method [5, 6].

In early literature, in stable patients, TTE was found to be accurate compared to the standard PA thermodilution technique [7–9], but in critically ill patients, predictability was found to be limited [10, 11].

With technological advancements, the ability of TTE to acquire high-quality images of critically ill patients improved [12, 13], and literature supporting the use of TTE to manage critical patients emerged [14–17].

Simultaneously, emerging literature supports the use of echocardiography for the measurement of cardiac output and its role in hemodynamic optimization [18–21].

In current literature, TTE is documented as a reliable, accurate, and highly valuable method to measure cardiac output, which provides rapid and vital diagnostic information and thereby guides clinicians for a wiser therapeutic strategy [6, 22–25].

Recent literature also documented that cardiac output measurement by transthoracic echocardiography was comparable to cardiac output measured by a pulmonary artery catheter thermodilution (TD) technique. Due to its wide availability, great potential to guide therapy, and noninvasive nature, TTE has become a routine and standard practice for bedside cardiac output measurement in the management of critical patients [26, 27].

How to measure and calculate cardiac output by TTE?

Parameters determined for the calculation of cardiac output by TTE are:

- Left ventricular outflow tract velocity time integral (LVOT VTI): Velocity-time integral (VTI) is measured by pulsed wave doppler signal, most commonly at the level of the left outflow tract (LVOT) obtained in the apical 5 chamber view. LVOT-VTI reflects the column of blood that moves through the left ventricle (LV) outflow tract during each systole; therefore, it is a TTE parameter representing stroke volume.
- Cross-sectional area (CSA): Measure the diameter of the LVOT in the parasternal long axis view in systole and calculate the area of the circle.
- Heart rate (HR).

Calculation of cardiac output: After obtaining the above parameters by TTE, cardiac output is calculated with the formula below:

Cardiac Output = Stroke Volume × HR

Cardiac Output =
[LVOT VTI × LVOT CSA)] × HR

To measure cardiac output precisely, averaging three measurements within one TTE examination is recommended in patients with sinus rhythm, and averaging five measurements is necessary for patients with atrial fibrillation [28].

Limitations of TTE are:

- Accuracy is highly dependent on an operator, so the possibility of inter-and intra-observer variability. But even non-cardiologist ICU physicians, after brief training, can accurately estimate cardiac output by TTE [23].
- The probe's position needs to be very accurate, and errors in position can lead to misinterpretations.
- The accuracy of TTE to measure cardiac output is unreliable in patients with high cardiac output, low sedation, or with physiological structural changes.
- TTE provides only intermittent and not continuous cardiac output measurements.

TTE, in addition to calculating cardiac output, measures inferior vena cava diameter and left ventricular size, identifies wall motion abnormalities, and assesses left and right ventricular function. By providing this information, TTE improves diagnostic accuracy, narrows the possible differential diagnosis of shock, and achieves volume status optimization. Small LV size, hyperdynamic LV (left ventricular end-diastolic area in the parasternal short axis view <10 cm2), or papillary apposition (kissing ventricles) are strongly indicative of hypovolemia and predicts fluid responsiveness [29, 30]. Papillary apposition can be false positive in LVH, vasodilatation and high inotropes.

B. Thoracic electrical bioimpedance and bioreactance

1. Thoracic bioimpedance

Thoracic electrical bioimpedance (TEB) is a non-invasive method to continuously estimate cardiac output using pairs of high-frequency but low-voltage disposable electrodes placed on either side of the neck and the lateral aspect of the chest wall.

The fluid offers less resistance to electric flow. A greater volume of blood column during each systole will work as a larger electrical contrast medium, lowering the electrical impedance. This principle is used to calculate stroke volume [31].

A series of signals from sensing electrodes will travels through the thorax and will continuously and accurately measures the cyclic changes in thoracic electrical impedance, which occurs due to changes in intrathoracic blood volume with each heartbeat. Based on these changes in electrical impedance, cardiac output is calculated.

The reliability of TEB is poor in the exact measurement of cardiac output in surgical and critically ill patients [32, 33].

However, as TEB measures cardiac output continuously and non-invasively, its use is rapidly increasing as a bedside cardiac output trend analysis monitor [34, 35].

Thoracic bioimpedance is a simple, easy-to-use, totally safe, and low-cost method that provides rapid, real-time, continuous, and automated cardiac output monitoring. Various factors that can affect the measurement of cardiac output by this method are electrical interference, cardiac arrhythmias, pleural effusions, pulmonary edema, chest tubes, internal or external pacemakers, or patient movement.

2. Thoracic bioreactance

Thoracic bioreactance is a modified, improved bioimpedance technology which measures time delay called a phase shift in alternating current voltage across the thorax rather than changes in impedance.

Electrodes applied on either side of the chest detect phase shifts, which almost exclusively depend on pulsatile flow (e.g., blood flow) but are less affected by static fluids (e.g., intravascular and extravascular fluids), electrical noise, patient movement, electrode positioning, and respiratory effort. In addition, because of newer technology-related improvements in the signal-to-noise ratio, bioreactance is theoretically superior to bioimpedance [36].

Thoracic bioreactance is found to be a reliable technique to measure cardiac output in many studies (but not in all studies) [37–41]. In a recent meta-analysis of the accuracy and precision of non-invasive cardiac output monitoring devices, percentage errors were 42% for bioimpedance and bioreactance [42].

Applanation tonometry and volume clamp method

Radial artery applanation tonometry and volume clamp method are two non-invasive uncalibrated techniques that provide continuous blood pressure monitoring and real-time cardiac output from the pulse contour analysis.

C. Radial artery applanation tonometry

In this method, the transducer is strapped over the radial artery with a bone underneath. Optimal pressure is adjusted to flatten the artery, and using an electromechanically driven sensor; continuous arterial pressure waveform is recorded. Then, cardiac output is estimated with the help of autocalibrating pulse contour analysis.

As this novel method is extremely easy to use, and its initial clinical data are promising, it is an attractive alternative to measure cardiac output in practice [43, 44]. However, evidence suggests that this method is not suitable for measuring cardiac output in hemodynamically unstable critically ill patients [45–47].

D. Volume clamp method

In this technique, a non-invasive pulse oximeter using finger cuff devices continuously measures cardiac output and finger arterial blood pressure in addition to peripheral oxygen saturation [48].

This method is an extension of conventional photoplethysmography whereby using an inflatable cuff at the finger, the digital arterial waveform is obtained. With a photodiode device, the diameter of the artery in the finger is measured. By adjusting the pressure in the cuff, the diameter of the artery is kept constant during pressure waveform analysis. Arterial pressure waveform is continuously recorded from the pressure changes in the cuff, and cardiac output is calculated.

This simple and convenient method for cardiac monitoring is promising in surgical and non-critical cases [49–51], but its use is discouraged in obese, cardiac surgery, and ICU patients because of poor accuracy [52–57].

This method is not suitable for patients with gross peripheral edema or severe peripheral vasoconstriction.

MINIMALLY INVASIVE AND INVASIVE SYSTEMS FOR CARDIAC OUTPUT MONITORING

Minimally invasive and invasive methods for cardiac output monitoring are used in hemodynamically unstable patients in intensive care and perioperative medicine when initial resuscitation measures fail to improve the patient’s hemodynamic and/or respiratory status. Accurate measurement of cardiac output with advanced hemodynamic monitoring will guide appropriate management with fluid resuscitation, vasopressors, or inotropic agents.

MINIMALLY INVASIVE SYSTEMS

Minimally invasive techniques commonly used for measuring cardiac output are transesophageal echocardiography, transpulmonary thermodilution, arterial pulse contour analysis, and partial CO2 rebreathing [58].

A. Transesophageal echocardiographic

Transesophageal echocardiography (TEE) is a minimally invasive technique to measure cardiac output. This method is widely used for diagnosing and monitoring critical and perioperative patients.

Technique

In TEE ultrasonic probe is placed into the esophagus under sedation. Placement of the TEE probe is similar to the insertion of a nasogastric tube, and the depth of the tube inserted in the esophagus is to place the tip of the probe at descending thoracic aorta level (between the fifth and sixth intercostal space), which will be roughly 35–45 cm mark on the probe.

TEE probe obtains a doppler flow signal and measures the blood velocity in the descending thoracic aorta. From different data obtained, such as heart rate, peak velocity, flow time corrected (FTc), and others, hemodynamic monitor derives cardiac output, Stroke volume, and systemic vascular resistance.

The use of TEE is expanding with growing technology [59]. In addition to standard 2D technology, TEE probes are available with different modalities such as doppler, pulse wave doppler, continuous wave doppler, color flow doppler, and 3D echocardiography.

Use

TEE plays a vital role in the management of perioperative and critical patients by providing valuable diagnostic and therapeutic information such as:

- Assessment of the volume status (detects hypovolemia early or excludes volume overload).
- Serve as a dynamic parameter to assess fluid responsiveness and guides clinicians for fluid management (i.e., goal-directed fluid therapy).
- Measures cardiac output, detects ventricular dysfunction, and diagnose coexisting problems like valvular structural and functional abnormalities, pericardial effusion, and cardiac tamponade.

The results of studies about the reliability of TEE in predicting cardiac output were conflicting [60, 61]. However, in a recent systematic review and meta-analysis, cardiac output measurement by TEE was accurate [27].

Advantages

Different advantages of TEE are:

- Provides superior quality image, accurate assessment of heart and great vessels, and greater diagnostic accuracy than transthoracic echocardiography because the probe is much closer to the heart, and bone and lung tissue do not interfere with imaging [62].
- As the TEE probe is just adjacent to posterior cardiac structures, TEE provides its superior quality image. On the contrary, the point of examination of the TTE transducer is more distant from the posterior

cardiac structures, i.e., at the anterior aspect of the chest. Therefore its visualization by TTE is poor.

- TEE monitoring does not disturb the surgical field and ensures continuous imaging in all stages of surgery [63].
- TEE is less dependent on the operator than TTE.

Indications

As TEE provides valuable information about several structural, functional, and hemodynamic parameters, its use is gaining popularity. But TEE is a semi-invasive method and therefore is used selectively when TTE cannot provide the required information, and the potential benefits of TEE outweigh the possible risks. Common indications of TEE are [62, 64–66]:

a. Intraoperative/Perioperative

TEE is indicated in high-risk surgical patients (e.g., significant coronary artery disease or poor cardiac status), patients with a risk of intraoperative hemodynamic instability (e.g., major vascular or abdominal surgery), major cardiac surgery like the repair of congenital heart lesions, repair of valvular lesions or thoracic aortic procedures, and as a rescue TEE in unexpected or unexplained hemodynamic unstable patients.

TEE monitoring and TEE-guided optimization of fluid administration improve outcomes, reduce postoperative complications, and shorten hospital stay in patients undergoing major or high-risk surgery [67–69].

b. Critically ill patients

TEE is useful in hemodynamically unstable critically ill patients because it calculates cardiac output, provides excellent visualization of cardiac structures, and is less dependent on the operator. TEE is used selectively in sedated ICU patients, usually on a mechanical ventilator [70]:

- For the assessment of unexplained persistent hypotension or hypoxemia when TTE or other modalities cannot obtain diagnostic information.
- For assessing volume status and cardiac output during fluid administration when no other hemodynamic monitoring systems are available.

c. Diagnostic modality

TEE is useful in diagnosing wall motion abnormalities, pericardial effusion, pulmonary hypertension, potential cardiac source of embolus, assessing valves for endocarditis, or excluding thrombi in patients with atrial fibrillation.

Contraindications

TEE's potential contraindications are previous esophagectomy, tracheoesophageal fistula, postesophageal surgery, esophageal trauma, esophageal pathologies such as varices, diverticulum, stricture or tumor; coagulopathy, thrombocytopenia, upper gastrointestinal bleeding, and hiatus hernia [70, 71].

Limitations

Although TEE is more useful than TTE, it is used in selected indications and not used routinely. TEE is used more frequently in the operating theater than in the ICU [72]. Limitations of TEE are:

- The minimally invasive technique (usually needs tracheal intubation, under sedation).
- Do not calculate cardiac output continuously compared to other hemodynamic monitoring devices, such as the pulmonary artery catheter (PAC) or transpulmonary thermodilution.
- Movement of the patient can change the position of the probe, and repositioning becomes necessary.
- Higher cost, time-consuming method (compared to TTE), can be performed

only on one patient at a time and needs cleaning and disinfection after each use.

- Do not measure blood pressure, so critical patients need an additional device for continuous blood pressure measurement.

B. Transpulmonary thermodilution

Transpulmonary thermodilution (TPTD) is a minimally invasive technique (requires two catheters, a central venous catheter, and an arterial line), which is considered a new gold standard in measuring cardiac output [2, 73]. This advanced diagnostic modality using two distinct techniques, transpulmonary thermodilution and pulse contour analysis, provides continuous cardiac output measurements.

Technique

A bolus of a cold solution of known temperature is injected rapidly into the superior vena cava through an internal jugular or subclavian central venous catheter. The injected solution will mix with blood and traverse through the right heart chambers, pulmonary circulation, and finally, through the left heart chambers reaches the systemic artery.

An arterial cannula placed in a large peripheral artery (femoral, axillary, or brachial artery) with a thermistor tip will sense and measure the drop in blood temperature across the cardiopulmonary system [74]. Temperature fall between the injection site and measurement site is inversely proportional to cardiac output. Using a change in blood temperature over time, computer software plots a thermodilution curve and calculates cardiac output and other relevant hemodynamic parameters.

Calculation of cardiac output by transpulmonary thermodilution intermittently calibrates pulse contour analysis, and therefore TPTD provides precise, continuous, and real-time measurement of cardiac output by taking advantage of both techniques [74].

Use

Valuable information provided by TPTD is [74]:

- Cardiac output: TPTD calculates cardiac output and stroke volume by analyzing an arterial pulse contour waveform. TPTD is a reliable method for the continuous and real-time monitoring of cardiac output [75]. This method also measures stroke volume variation (SVV)/PVV and predicts fluid responsiveness [76].
- TPTD is also helpful in measuring various parameters such as, global end-diastolic volume, cardiac function index and global ejection fraction, extravascular lung water index, pulmonary vascular permeability index, which helps in assessment of volume status [74, 77–82].

Advantages

Transpulmonary thermodilution is used more frequently and has replaced the conventional intermittent thermodilution (TD) method through PAC to calculate cardiac output because:

- TPTD method is less invasive and avoids PAC-related serious complications [74].
- TPTD measures cardiac output with the same accuracy and is interchangeable with PAC thermodilution [83–86].
- It provides continuous and real-time monitoring of cardiac output in contrast to intermittent measurement by the conventional TD method.
- Provides robust support in the therapeutic management of hemodynamically unstable patients by

providing several additional information such as measurement of SVV and pulse pressure variation (PPV) to predict fluid responsiveness, calculates extravascular lung water to quantify pulmonary edema, and estimates lung permeability to quantify the pulmonary leak [82].

Indications

This advanced but invasive hemodynamic monitoring is indicated over less invasive devices in selected most critically ill and/or complex patients such as:

- Perioperatively, during complex cardiac and prolonged major surgery.
- During major liver surgery, when less invasive techniques are unreliable [87].
- In ICU patients with severe shock, especially with acute respiratory distress syndrome, and high or increasing requirements of vasopressors [4, 72]. In ICU patients with severe shock, especially with acute respiratory distress syndrome, and high or increasing requirements of vasopressors [4, 72].

Limitations

- It is an invasive method that needs the placement of a central venous line and a large arterial line.
- This method does not provide information such as PA pressure and SvO_2 (unlike the PA thermodilution method).
- Needs manual calibration with cold water.
- It provides inaccurate measurements in patients with very low cardiac output (<2 L/min) [74].
- Unable to detect short-term hemodynamic changes induced by ventilation during passive leg raising or end-expiratory occlusion tests [74].

C. Lithium dilution

The lithium dilution technique is a minimally invasive method that measures cardiac output based on indicator dilution principles [88].

In this modality, a small dose of lithium is injected via any vein (peripheral vein or central), and a lithium-selective sensor connected to any peripheral arterial line (e.g., radial artery) measures the concentration of lithium ions in the arterial blood [89]. The lithium dilution curve (lithium concentration vs. time) is constructed, and cardiac output is derived from this data.

Lithium dilution is a less invasive method than transpulmonary thermodilution. It is performed using peripheral venous and arterial cannulation and, therefore, is without the risks of the pulmonary artery or central venous catheterization [90]. This method can measure cardiac output accurately [91].

Lithium is selected as an indicator for this dilution technique because this element is not found in the bloodstream; it is non-diffusible; a small dose is non-toxic but generates a plasma concentration that can be measured.

Lithium is not lost during the first pass in pulmonary circulation, so its assessment provides reliable value. Additionally, lithium is cleared rapidly from systemic circulation [92].

Avoid this technique during pregnancy and in patients weighing less than 40 kg, receiving lithium therapy, or high doses of nondepolarizing neuromuscular blockers [93].

D. Arterial pulse contour analysis

Arterial pulse contour analysis is a commonly used minimally invasive technique for continuous, beat-to-beat cardiac output measurement. Based on it, a computerized algorithm measures cardiac output.

In addition to cardiac output, arterial pulse contour analysis also calculates dynamic parameters such as pulse pressure variation and stroke volume variation, which is helpful for determining fluid responsiveness [4].

Several commercially available devices use pulse contour wave analysis for the continuous measurement of cardiac output and stroke volume. These devices are broadly divided into two groups, the calibrated (PiCCO Plus and LiDCO plus) and the uncalibrated systems (FloTrac/Vigileo and LiDCO rapid), as summarized in Table 19.1.

The advantages of the pulse contour analysis method are:

- Less invasive compared to cardiac output measurement by pulmonary artery catheter and transpulmonary thermodilution, as it requires only a peripheral arterial catheter (usually the radial artery).
- Easy method: An arterial line is frequently inserted in ICU so existing access can be utilized for pulse contour analysis.
- Continuously and real-time measurement of cardiac output.
- Effectively monitor volume responsiveness. In addition to the accurate measurement of stroke volume, cardiac output, and CI, pulse contour analysis also calculates dynamic indexes such as pulse pressure variation and stroke volume variation. These parameters help to determine response to a fluid challenge, passive leg raising, or end-expiratory occlusion in patients on a ventilator [4, 76].
- Operator independent and needs minimal training.

Limitations of arterial pulse contour wave analysis are:

- It is a less accurate technique in critically ill patients with low SVR (sepsis and chronic liver failure) [94], left ventricular dysfunction [95], norepinephrine infusion [96], in open aortic abdominal aneurysm repair [97], and off-pump coronary artery bypass surgery [98].
- An accuracy of PCA is low in patients with spontaneous breathing, cardiac arrhythmias, low tidal volume ventilation, positive-end expiratory pressure <5 mmHg, or abnormal abdominal pressure [99].
- Data suggesting that this device improve patient outcome are lacking [100, 101].
- This method is less reliable than the transpulmonary thermodilution technique in septic patients [102].
- The uncalibrated systems need frequent recalibration in patients with hemodynamic instability or requiring vasoactive drugs.

E. Partial CO_2 rebreathing

Partial CO_2 Rebreathing is a minimally invasive technique which uses indirect Fick's principle to calculate cardiac output [103]. This method can be used only in intubated, sedated patients on volume-controlled ventilation who are hemodynamically stable.

This technique is easy to use, safe, does not require a PAC, can be repeated every few minutes without substantial risk of CO_2 accumulation, and provides almost continuous cardiac output measurements.

This technique's accuracy and precision are similar to esophageal doppler ultrasound, pulse contour analysis, and thoracic bioimpedance [33].

Currently, this technique is mainly focused on short-term intraoperative applications or mechanically ventilated postoperative patients [104].

This modality is not used routinely in ICU because its predictability is poor in common problems in critical patients like hemodynamic instability, anemia, or significant pulmonary disease (such as acute respiratory distress syndrome, pneumonia, atelectasis, shunting, etc.). Additionally, it does not provide information about the intravascular volume status or fluid responsiveness [105].

Avoid using this technique in patients with severe hypercapnia, raised intracranial pressure, or pulmonary hypertension because arterial CO_2 tension rises transiently in the rebreathing period, which may be harmful [106].

INVASIVE SYSTEMS

Pulmonary artery thermodilution is an invasive technique frequently used for hemodynamic monitoring.

Pulmonary artery thermodilution

Cardiac output measured invasively with the pulmonary artery using the thermodilution principle is traditionally considered as a gold standard method [107]. Modalities to measure cardiac output by pulmonary thermodilution (TD) are divided into two types: intermittent bolus and continuous cardiac output methods.

1. Intermittent thermodilution using the "bolus" technique

In the bolus technique of pulmonary thermodilution, about 10 ml of cold saline solution is injected via the proximal lumen of PAC in the right atrium. Cold saline mixes adequately with surrounding blood while traversing from the right atrium to the pulmonary artery (by passing through two valves and a right ventricle), which decreases blood temperature transiently. A thermistor on the tip of the PAC senses and measures changes in the blood temperature over time at a downstream side in the pulmonary artery [84].

The fall in the temperature is inversely proportional to the blood flow and cardiac output. Electronic monitors calculate cardiac output using a modified Stewart–Hamilton equation [108]. Usually, three measurements are performed and averaged to obtain a more reliable result [109].

Major advantages of the pulmonary artery thermodilution method are:

- Uses thermal energy (i.e., cold water) as an indicator which is non-toxic.
- Repeated measurement of cardiac output is safe, provided there is no constraint to administer the fluid.
- No requirement for manual calibration.
- The major advantage of this technique is that it provides an additional measurement of hemodynamic parameters such as pulmonary artery pressures, right-sided and left-sided filling pressures, and mixed venous oxyhemoglobin saturation (SvO_2).

Major limitations of the pulmonary artery thermodilution method are:

- The technique is invasive, so it carries the risk associated with placement and presence of a PAC, such as infection, pulmonary artery rupture, arrhythmias on insertion, thrombosis, and embolism [110].
- Fail to detect abrupt changes in cardiac output promptly because this technique measures cardiac output with some delay [107].
- Error in measuring cardiac output in the presence of low cardiac output,

hypothermia, shunts, and cardiac valvular abnormalities.

- Error in measuring cardiac output in the presence of low cardiac output, hypothermia, shunts, and cardiac valvular abnormalities [111].
- Poor predictor of fluid responsiveness [112].
- Need to avoid magnetic resonance imaging as well as the use of electrocautery in patients with PAC.

2. Continuous thermodilution technique

Commercially available catheters with newer technologies now provide continuous cardiac output monitoring. This method uses the same thermodilution principles but uses a warmed bolus rather than a cold bolus [113].

This special catheter has a special blood-warming thermal filament or coil at the level of the right ventricle. Thermal filament heats the blood in a semi-random binary fashion. The thermistor at the tip of the PAC records changes in temperature and calculates the cardiac output by thermodilution.

This method's major benefits are a continuous display of cardiac output, avoidance of repeated boluses (which reduces the risk of infection), and avoids operator errors [114].

Details about pulmonary artery catheters, including description, insertion technique, use in clinical practice, indications, and complications, are covered in the pulmonary artery catheter monitoring part of the Chapter 17 on "Static Hemodynamic Monitoring Techniques."

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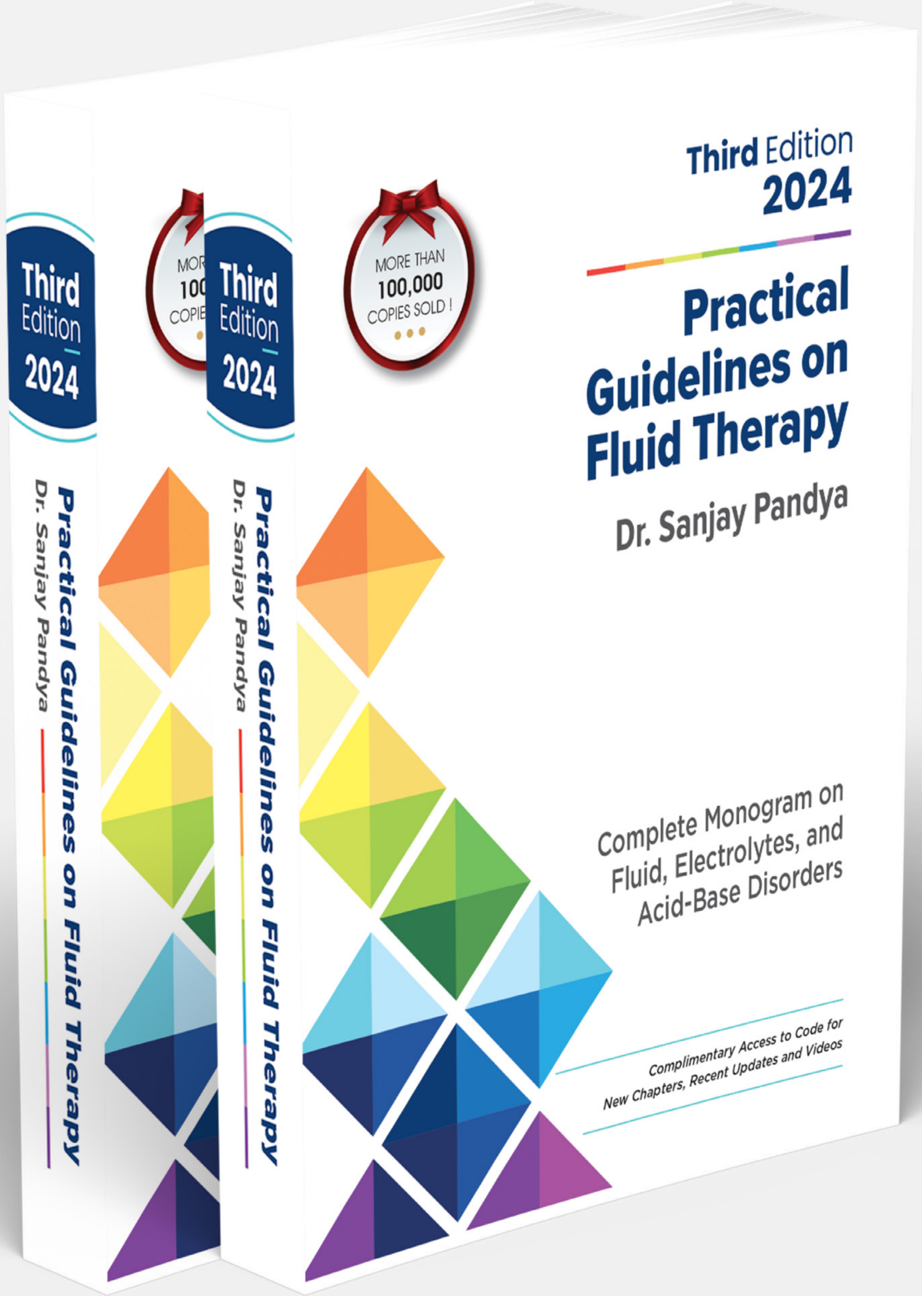
Chapter 20:

Hyponatremia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SODIUM PHYSIOLOGY

A basic understanding of physiology is essential for the proper approach and treatment of water balance and sodium balance disorders in clinical practice.

Water excess or deficit in the body leads to hyponatremia and hypernatremia. Therefore disorders of sodium concentration occur primarily due to water imbalance and not due to changes in total body sodium content. The below-mentioned equation will help to clarify the above statement.

$$\text{Serum Sodium Concentration} = \frac{\text{Total Body Sodium}}{\text{Total Body Water}}$$

In the above equation, serum sodium concentration will decrease when total body water increases, leading to hyponatremia. Similarly, serum sodium concentration will increase when total body water decreases, leading to hypernatremia. So, to understand sodium disorders, we need to know about the physiology of water balance.

As serum osmolality is determined mainly by sodium salts (equation below) [1], the regulation of water balance is also discussed as the regulation of body fluid osmolality (osmoregulation). Normal serum osmolality is 275–290 mOsm/kg. Hyponatremia is usually associated with low serum osmolality.

$$\text{Serum Osmolality (Calculated)} = 2\,[\text{Na}^{+}] + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8}$$

Where osmolality is in mOsm/kg, sodium in mEq/L, glucose in mg/dL, and blood urea nitrogen (BUN) in mg/dL.

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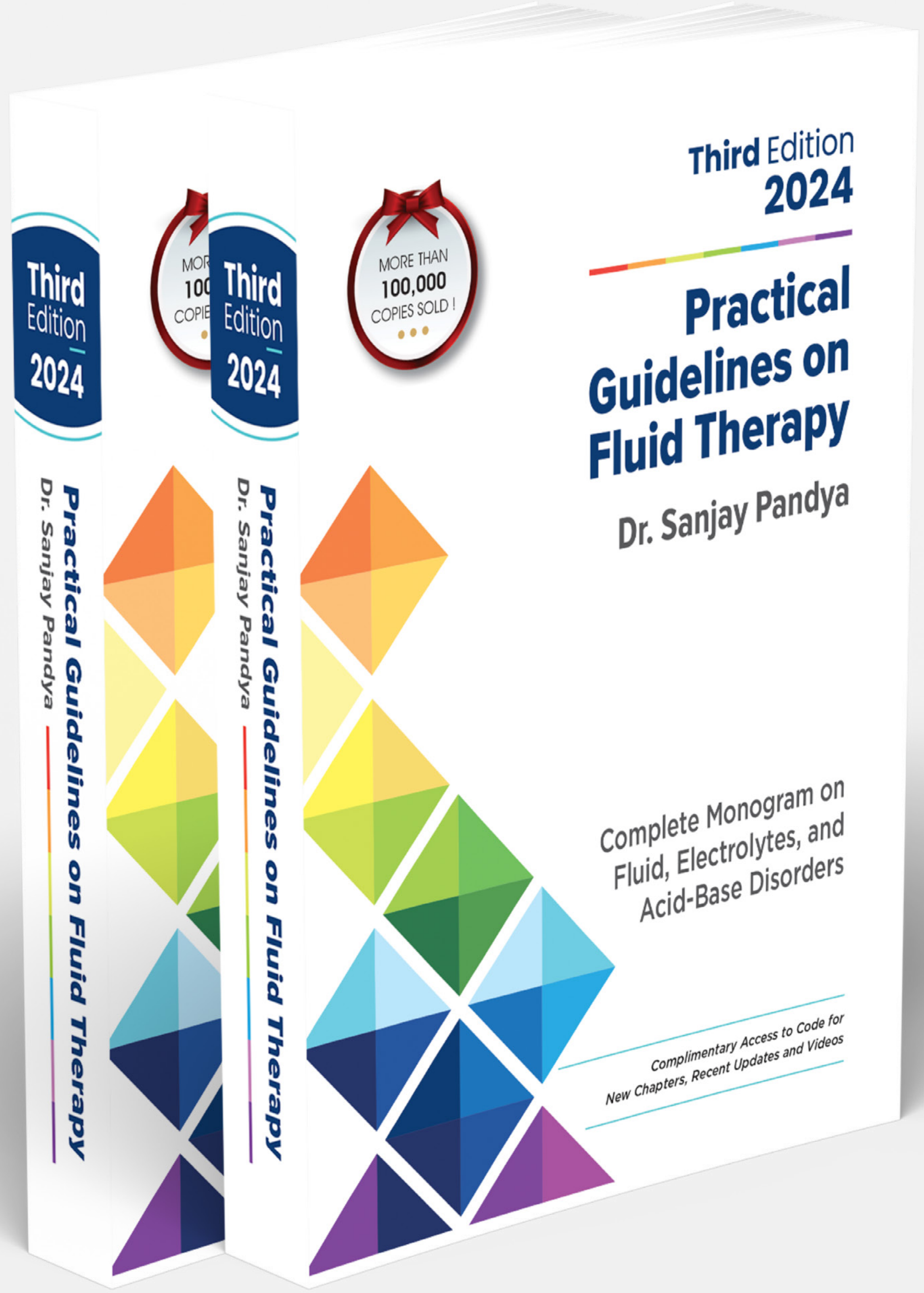
Chapter 21:
Hypernatremia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Hypernatremia

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Hypernatremia is an electrolyte disorder defined as an increase in plasma sodium concentration greater than 145 mEq/L, always results in hypertonicity (hyperosmolality), and usually occurs due to lack of water, loss of water, or primary sodium gain [1, 2].

Hypernatremia is a less frequent disorder (about 1%–3% of all hospitalized patients and 9% in critically ill patients) but carries significantly higher mortality (about 40–60%) [3–5].

HYPERNATREMIA IS USUALLY DUE TO WATER DEFICIT AND NOT SODIUM OVERLOAD.

Normal thirst is the most potent mechanism that effectively prevents hypernatremia. So, hypernatremia usually does not occur in healthy adults who can respond to thirst unless there is non-availability of water, restricted water intake, impaired thirst, or the patient cannot drink the water due to a comatose-confused state. Therefore, hypernatremia is seen chiefly in very young, very old, very sick, bed-ridden, or debilitated patients. A pure water deficit leading to hypernatremia is called dehydration.

ETIOLOGY

Common causes of hypernatremia classified based on volume status, water loss or salt gain, urinary sodium, and underlying etiologies are summarized in Table 21.1.

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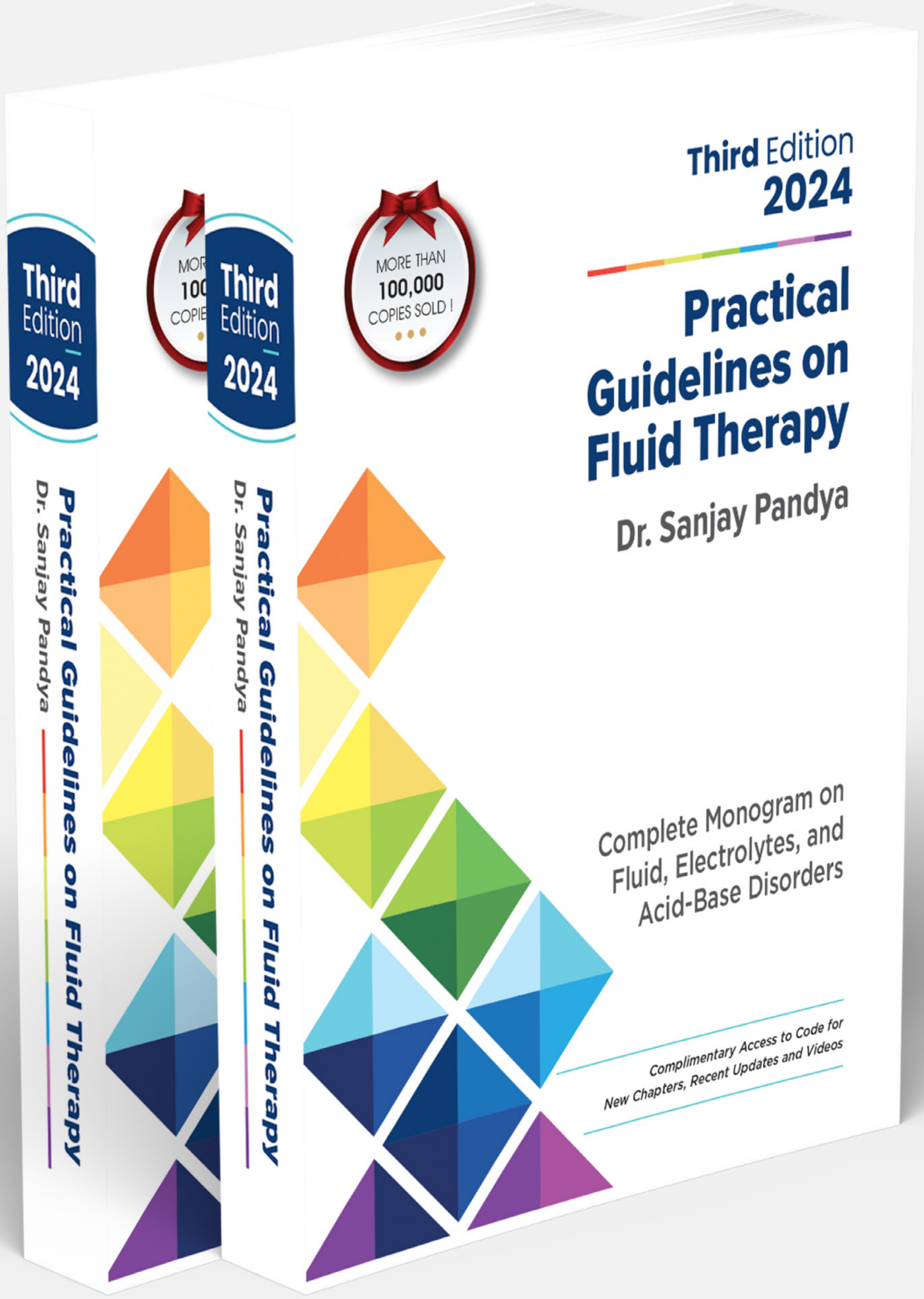
Chapter 22:
Hypokalemia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Hypokalemia

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POTASSIUM

PHYSIOLOGICAL BASIS

Potassium (K^+) is a major intracellular cation and the second most abundant cation in the body (next to cation sodium). Total body potassium is about 3,500 mEq. Out of this, 98% of potassium is intracellular, and just 2% of potassium is extracellular. Thus, the normal serum potassium concentration is 3.5 to 5.0 mEq/L vs. an intracellular 140 to 150 mEq/L.

Potassium plays a crucial role in the following:

- Normal functioning of cells: Synthesis of DNA and protein, cell division and growth, and enzyme function.
- Neuromuscular transmission: Maintaining cell membrane potential, cellular excitability, conduction of nerve impulses which help in maintaining skeletal, cardiac, and smooth muscle cell contraction.

- Regulate intracellular osmolality and cell volume.
- Maintain acid-base balance and regulate intracellular pH.

POTASSIUM HOMEOSTASIS

The average potassium intake is about 77 and 59 mEq per day in adult men and women, respectively [1]. 90% of potassium consumed is absorbed in the upper gastrointestinal (GI) tract, out of which kidneys excrete 90%, and the remaining 10% is excreted in the stool.

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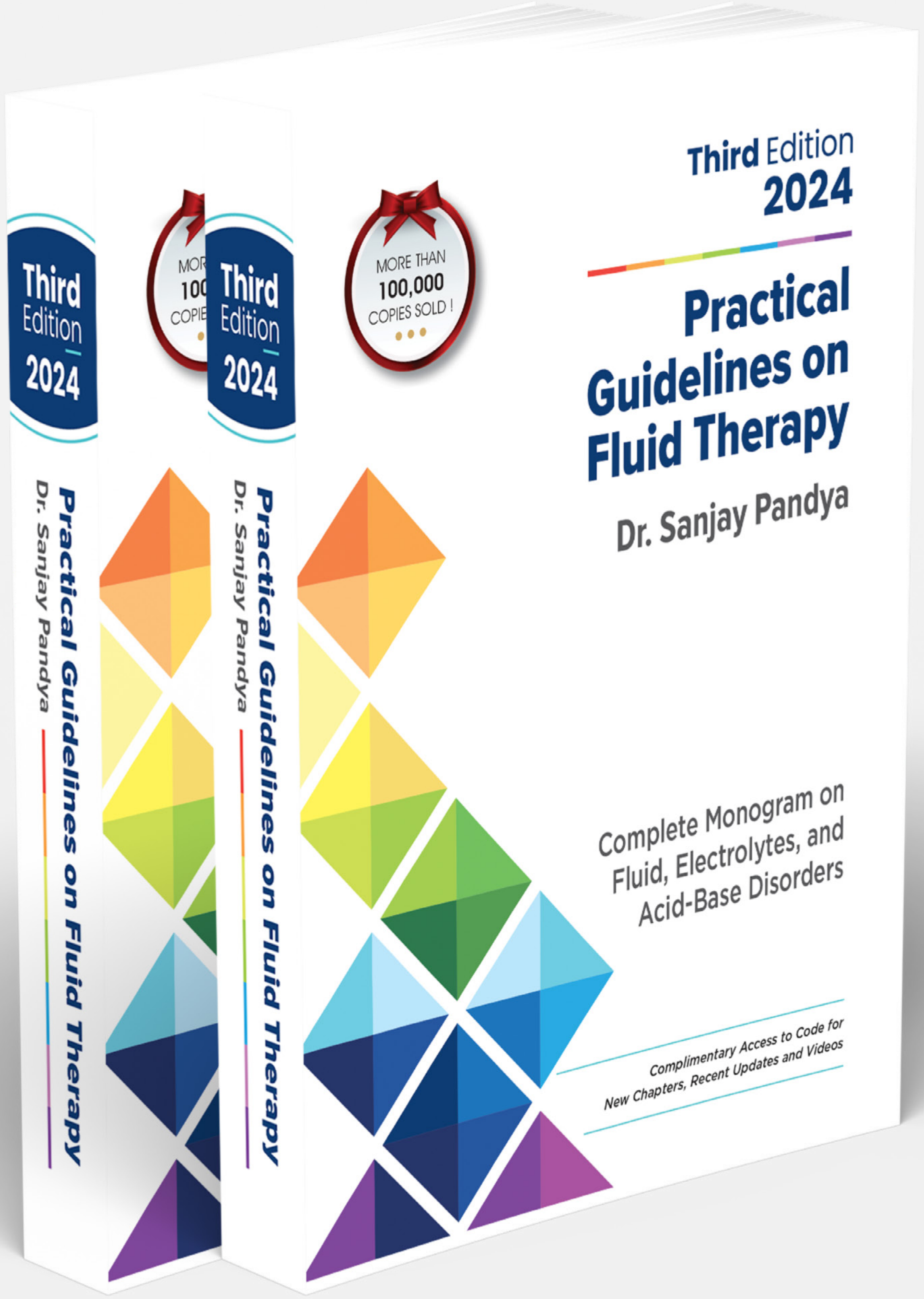
Chapter 23:

Hyperkalemia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A serum potassium level greater than 5.5 mEq/L is considered hyperkalemia. The incidence of hyperkalemia is very low in the general population but increases in patients with chronic kidney disease (CKD), heart failure, diabetes and in patients receiving renin-angiotensin-aldosterone system inhibitor (RAASi) treatment [1–5]. Hyperkalemia is a potentially life-threatening electrolyte disorder associated with significantly increased hospitalizations, cardiovascular events, and all-cause mortality [6–9]. In addition, acute severe hyperkalemia is a potentially dangerous problem that can cause cardiac arrhythmias leading to cardiac arrest and death.

ETIOLOGY

The most common causes of hyperkalemia are renal dysfunction (acute or chronic), medication causing impaired potassium excretion, diabetes mellitus, cell lysis (rhabdomyolysis, tumor lysis syndrome, massive hemolysis), and pseudohyperkalemia [10]. The causes of hyperkalemia based on its mechanism of development are summarized in Table 23.1.

CKD is the most common risk factor for hyperkalemia, and hyperkalemia is the most common electrolyte disturbance in CKD [11, 12]. Furthermore, as CKD advances, the prevalence of hyperkalemia increases [3, 13].

A. Drug-induced hyperkalemia

Various drugs interfere with potassium homeostasis and can cause hyperkalemia by affecting renal potassium excretion, inhibiting the renin-angiotensin-aldosterone system, or promoting the transcellular potassium shift from intracellular fluid (ICF) to extracellular fluid (ECF) compartment (Table 23.2. Drug-induced hyperkalemia) [10, 14, 15].

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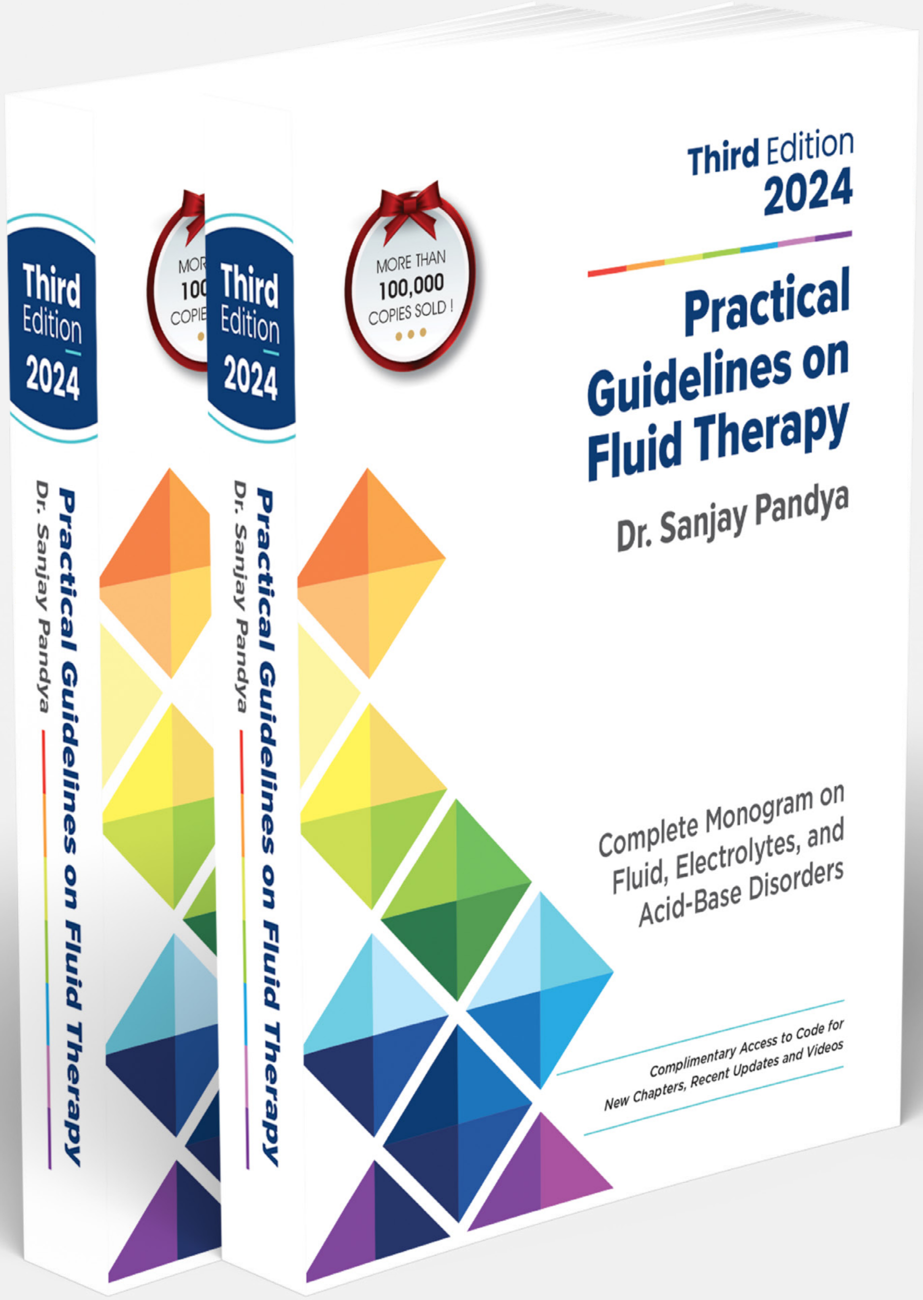
Chapter 24:

Hypocalcemia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BASIC PHYSIOLOGY

Calcium (Ca) is essential for bone formation, neuromuscular function, and blood coagulation. If calcium intake is inadequate, it may impair bone mineralization in children and accelerate bone loss in adults.

Distribution

An average adult's body contains 20 to 25 gm/kg or 1.2 to 1.4 kg of calcium, so it is the most abundant cation in the body. Out of this, about 99% is present in the bone, 1% in the soft tissue cells, and 0.15% in the extracellular fluid (ECF). As serum calcium concentration constitutes less than 1% of the total body calcium, it is a poor marker of overall total body calcium content.

Serum calcium

The normal value is about 8.5 to 10.5 mg/dL (4.3 to 5.2 mEq/L, 2.2 to 2.6 mmol/L).

The total ECF calcium exists in three forms:

1. Bound to proteins: About 40% of calcium is bound to protein (mainly albumin) which will not be diffusible and biologically active.
2. Free-ionized: 50% of calcium is in an ionized form which is diffusible and biologically active.
3. Bound to anions: 10% calcium is complexed with the anions of organic acids such as phosphate, bicarbonate, citrate, lactate, or sulfate phosphate. This form of calcium is diffusible but biologically inactive.

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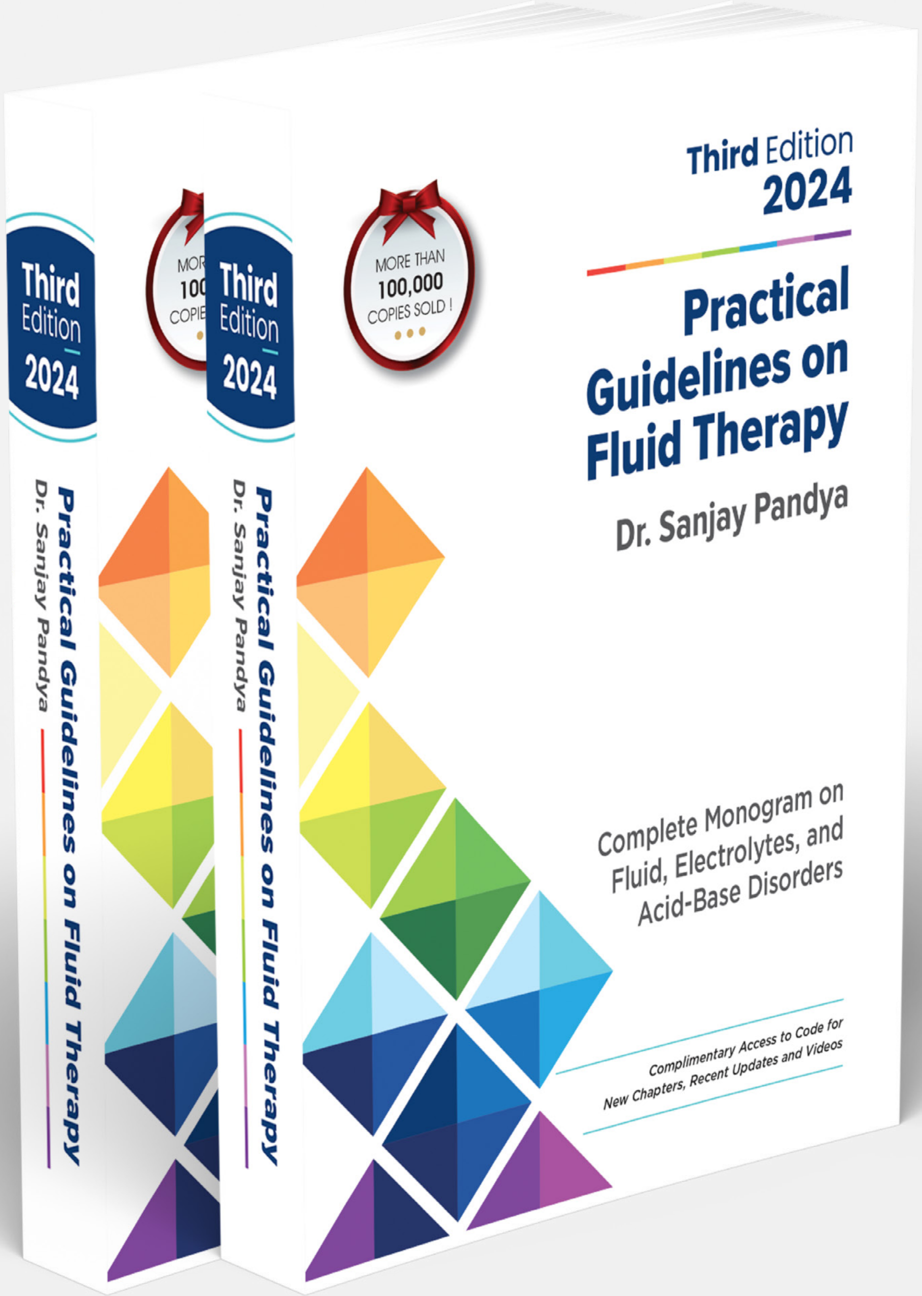
Chapter 25:

Hypercalcemia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Hypercalcemia is a less common disorder than hypocalcemia, occurring in about 0.6–7.5% of hospitalized and less than 1.0% of outpatients [1–6].

Hypercalcemia is defined as total serum calcium >10.5 mg/dL (>2.6 mmol/L) with normal serum albumin or ionized calcium >5.2 mg/dL (>1.3 mmol/L) [7].

When total serum calcium is >14.0 mg/dL (>3.5 mmol/L) or ionized calcium is >7.0 mg/dL (>1.7 mmol/L), it is considered severe hypercalcemia [7]. Early detection and prompt treatment of hypercalcemia are essential because it carries high morbidity and mortality [7, 8].

ETIOLOGY

Primary hyperparathyroidism and malignancy are the two most common causes of hypercalcemia in more than 90% of patients [7, 9]. In recent times, there has been a significant rise in hypercalcemia due to Vitamin D toxicity.

Mechanisms by which different etiologies cause hypercalcemia are enhanced bone resorption, increased intestinal absorption, or decreased renal calcium excretion (Table 25.1).

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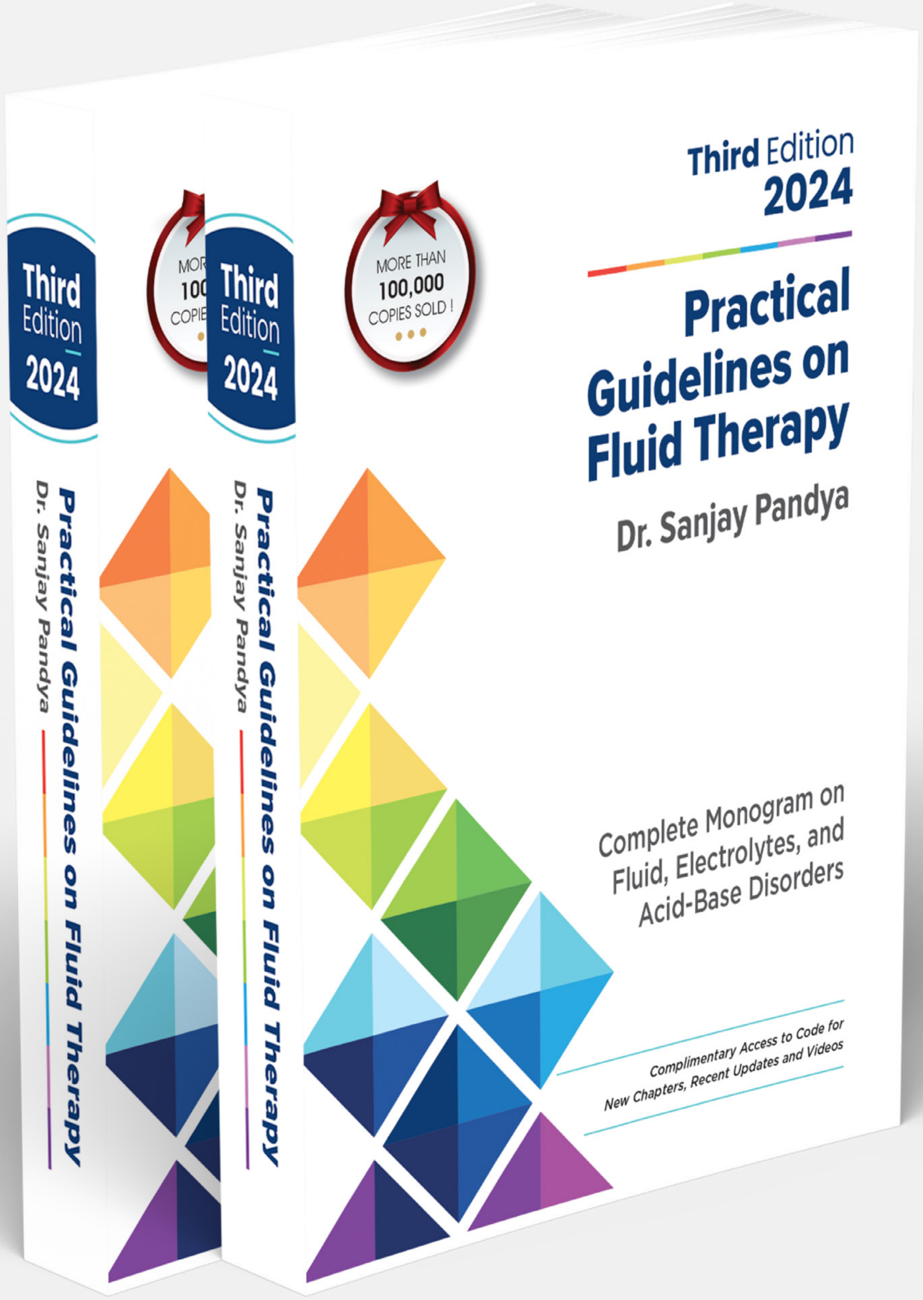
Chapter 26:

Hypophosphatemia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SERUM PHOSPHATE

Phosphorus is a vital component of all body tissues and plays an essential role in various body functions. The terms phosphate and phosphorus are commonly used interchangeably.

BASIC PHYSIOLOGY

- Phosphate is the most abundant intracellular anion, the second-largest mineral in the body after calcium, and comprises approximately 1% of the body weight.
- Distribution: Most (about 85%) of the body's phosphorus is found within bone and teeth as hydroxyapatite, and the rest is distributed in tissues throughout the body. As only 1% of total body phosphorus is found in the extracellular fluid (ECF), the value of serum phosphorus may not necessarily reflect total body phosphorus content. In addition, even a change in pH leads to a shift of phosphate (acidosis shifts phosphate from intracellular fluid (ICF) to ECF) and affects the value of serum phosphorus.
- Normal value: Normal serum phosphorus levels in adults range from 2.5 to 4.5 mg/dL (0.75 to 1.45 mmol/L). It is best measured in the fasting state since there is as much as 50% diurnal variation (lower value in the morning and higher at night and after meals). Clinically, serum phosphorus level reflects nutritional status.
- Function: Phosphorus plays a major role in bone formation and is involved in cellular energy metabolism for

almost all cellular functions (e.g., cell membranes, phospholipids, nucleic acids, acid buffering, enzyme systems, the energy carrier ATP-adenosine triphosphate, etc.).

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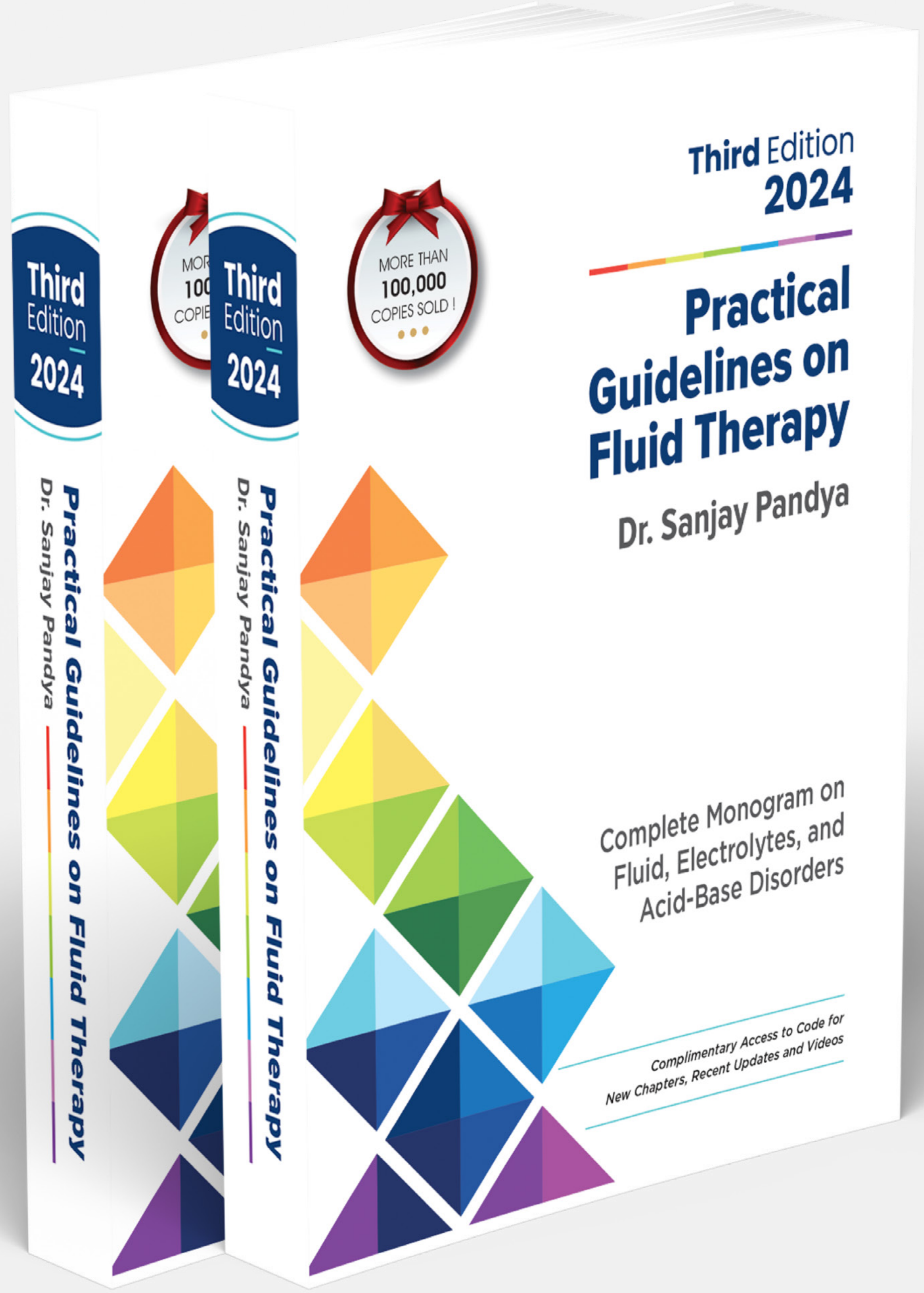
Chapter 27:

Hyperphosphatemia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Hyperphosphatemia

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Hyperphosphatemia is defined as serum phosphate concentration greater than 4.5 mg/dL (1.45 mmol/L) in adults.

Renal excretion of phosphate is very effective, and therefore the person with normal renal function is unlikely to develop hyperphosphatemia because of increased phosphate intake. Therefore, Hyperphosphatemia is rare in the general population but commonly occurs in later stages of chronic kidney disease (CKD) with significantly impaired kidney function [1].

ETIOLOGY

Based on the mechanism of its development, the causes of hyperphosphatemia can be classified into four groups [1].

Decreased renal phosphate excretion

- Impaired renal phosphate excretion: Acute kidney injury (AKI) or chronic kidney disease with significant renal impairment are the most common cause of hyperphosphatemia [2].
- Increased renal tubular reabsorption: Hypoparathyroidism, vitamin D toxicity, acromegaly or thyrotoxicosis.

Transcellular shift

Transcellular shift from intracellular fluid (ICF) to extracellular fluid (ECF)

- Extensive cell destruction: Rhabdomyolysis, tumor lysis syndrome, or massive hemolysis.

- Severe acidosis: Severe lactic acidosis, diabetic acidosis and respiratory acidosis.
- Lack of insulin: Diabetic ketoacidosis (before treatment).

Acute massive phosphate load

Administration of phosphate-containing laxatives or enemas and IV or oral phosphate administration.

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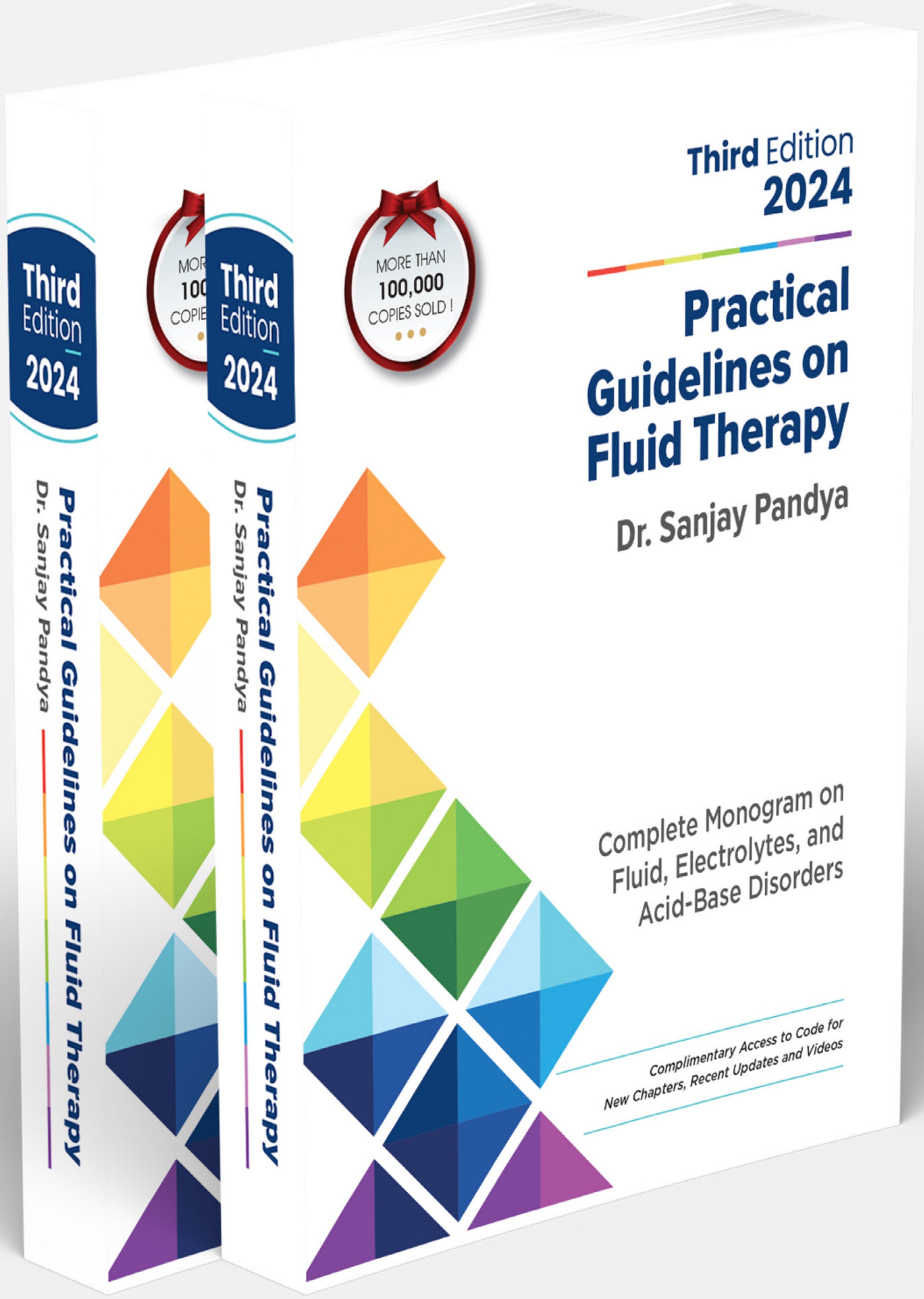
fluid

Chapter 28:

Hypomagnesemia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SERUM MAGNESIUM

Disorder of magnesium, especially hypomagnesemia, is expected particularly in ICU patients and usually occurs due to renal and gastrointestinal (GI) losses. However, hypermagnesemia is a less frequent disorder than hypomagnesemia, and its most common cause is renal failure.

BASIC PHYSIOLOGY

- Magnesium is the fourth most common cation of the body (after Na$^+$, K$^+$, and Ca^{2+}), the second most common intracellular cation (after K$^+$), and the commonest intracellular divalent cation.
- **Distribution:** About 60% of body magnesium is in bones, 39% is within the cells, and only 1% is in extracellular fluid (ECF). Up to 40% of total plasma magnesium is protein-bound, 5–10% is in complex form, and about 50–55% is in a free, ionized form, which is a biologically active ion (like calcium).

Table 28.1 Interpretation of serum magnesium concentration

Hypomagnesemia			Normal range	Hypermagnesemia		
Severe	**Moderate**	**Mild**		**Mild**	**Moderate**	**Severe**
<1.0 mg/dL	1.0-1.5 mg/dL	1.6-1.9 mg/dL	1.7-2.1 mg/dL	4.8-7.2 mg/dL	7.2-12 mg/dL	>12 mg/dL
<0.5 mmol/L	0.4-0.6 mmol/L	0.7-0.8 mmol/L	0.70-0.85 mmol/L	2.0-3.0 mmol/L	3.0-5.0 mmol/L	>5 mmol/L
<0.8 mEq/L	0.8-1.2 mEq/L	1.4-1.6 mEq/L	1.4-1.7 mEq/L	4.0-6.0 mEq/L	6.0-10 mEq/L	>10 mEq/L
Conversion factors for serum magnesium: 1 mEq/L = 1.2 mg/dL = 0.5 mmol/L						

- **Normal blood ranges:** The normal serum magnesium level is 1.7 to 2.1 mg/dL (0.70 to 0w.85 mmol/L, 1.4 to 1.7 mEq/L), and their values in magnesium disorders are summarized in Table 28.1.
- As the clinical effects of magnesium disorders are determined primarily by tissue magnesium content, serum magnesium levels have limited diagnostic value.

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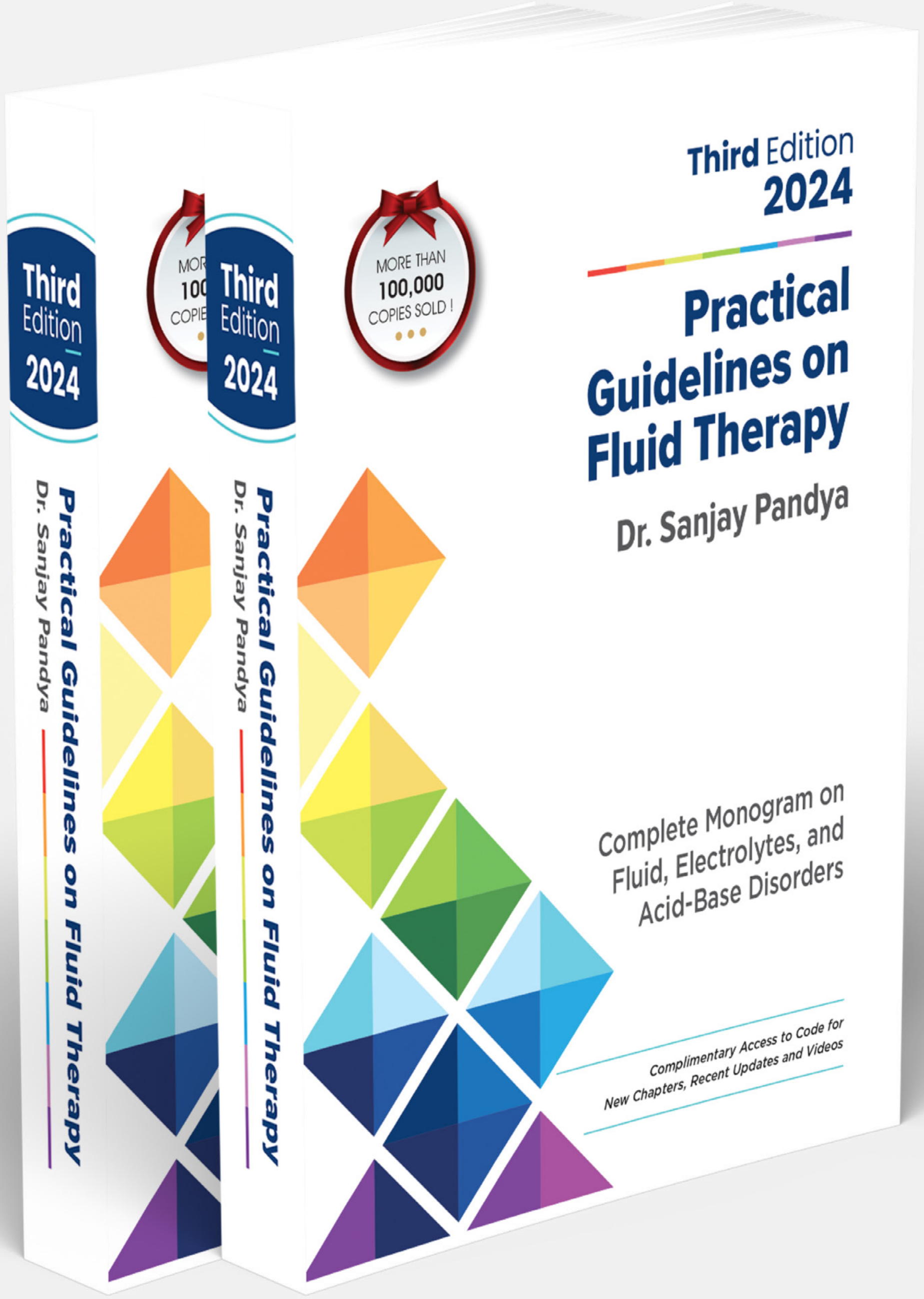
Chapter 29:

Hypermagnesemia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Hypermagnesemia is an uncommon electrolyte disorder defined as serum magnesium concentration above 2.6 mg/dL (1.1 mmol/L, or 2.14 mEq/L). As a normal kidney can effectively excrete magnesium load, hypermagnesemia is rarely seen in clinical practice if renal function is normal.

ETIOLOGY

Hypermagnesemia is frequently iatrogenic and almost always occurs either due to impaired excretion of magnesium in acute kidney injury (AKI) or chronic kidney disease (CKD) or the administration of magnesium in a large amount [1–4].

Common causes are:

- Renal failure: AKI or CKD patients receiving magnesium-containing antacids, laxatives, or IV fluids [3, 5, 6].
- Excessive magnesium intake: Treatment of preeclampsia or eclampsia with IV magnesium sulfate, aggressive treatment of hypomagnesemia with IV magnesium, intake of large amounts of magnesium salts as cathartics or antacids, and use of rectal magnesium sulfate enemas.
- Compartment shift or leak: Diabetic ketoacidosis untreated, tumor lysis syndrome, acute rhabdomyolysis, hemolysis, and severe burns.
- Miscellaneous causes: Milk-alkali syndrome and impaired renal excretion of magnesium due to primary hyperparathyroidism, adrenal insufficiency, and hypothyroidism.

CLINICAL FEATURES [7, 8]

Symptoms of hypermagnesemia are chiefly neuromuscular, cardiac, and related to hypocalcemia, which varies as per the magnesium level and, in severe form, can be serious and potentially fatal, as summarized in Table 29.1.

Neuromuscular manifestations: Hypermagnesemia inhibits acetylcholine release from the neuromuscular endplate, causing the blockage of neuromuscular transmission leading to a neuromuscular symptom. It includes muscular weakness, lethargy, loss of deep tendon jerks, muscular paresis leading to respiratory depression, respiratory failure, and quadriparesis. In addition, due to smooth-muscle paralysis, hypermagnesemia may present as paralytic ileus or urinary retention.

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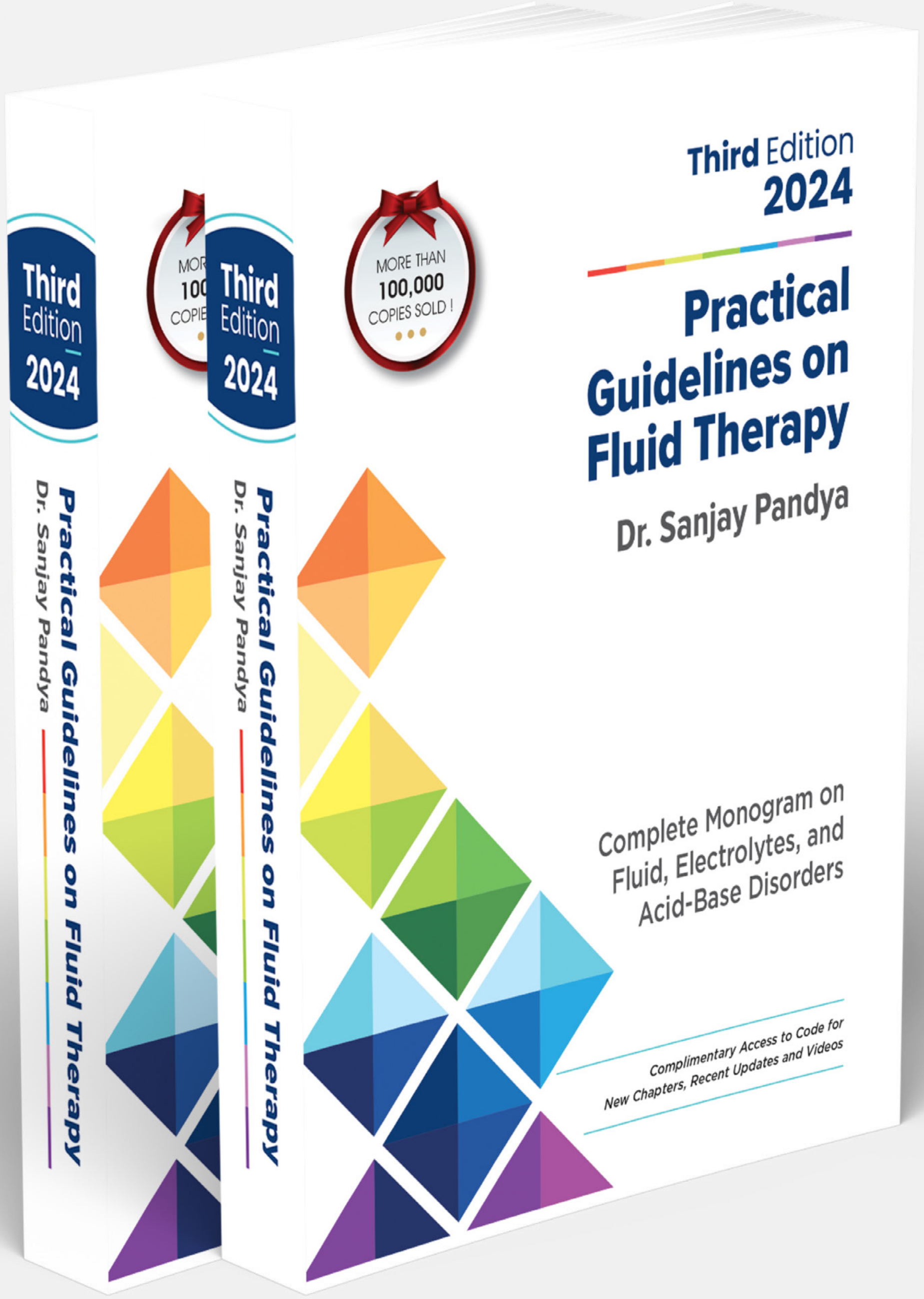
Chapter 30:

Basic Understanding and Approach to Acid-Base Disorders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Arterial blood gas (ABG) measurements are a crucial diagnostic test in medicine, providing vital insights for diagnosing acid-base disorders and guiding life-saving treatments in critically ill patients. Acid-base disorders frequently manifest in critically ill patients and can also serve as initial indicators of underlying diseases, such as Kussmaul's breathing presenting in diabetic ketoacidosis or renal failure.

To clearly understand the subject and its approach, this chapter outlines basic terminology, the physiology of pH regulation, compensation in various acid-base disorders, and the diagnostic approach.

UNDERSTANDING BASIC TERMINOLOGY

Basic terminology used to discuss acid-base disorders and their values in simple acid-base disorders are summarized below (Table 30.1).

pH: pH represents the concentration of free hydrogen ions (H^+). It has an inverse relationship with H^+ ion concentration. The normal value of pH in arterial blood is 7.4 (7.35–7.45).

Acid, acidemia and acidosis

- A decrease in pH indicates an increase in H^+ ion concentration.
- An acid is a substance that can donate H^+ ions or, when added to a solution, increase the H^+ ion concentration, thereby lowering the pH.
- An acidemia, which refers to "acid blood", is characterized by a blood pH below normal (pH <7.35) and an increased H^+ ion concentration.
- Acidosis is an abnormal process or disease that reduces pH (pH <7.35) due to an increase in acid or a decrease in alkali.

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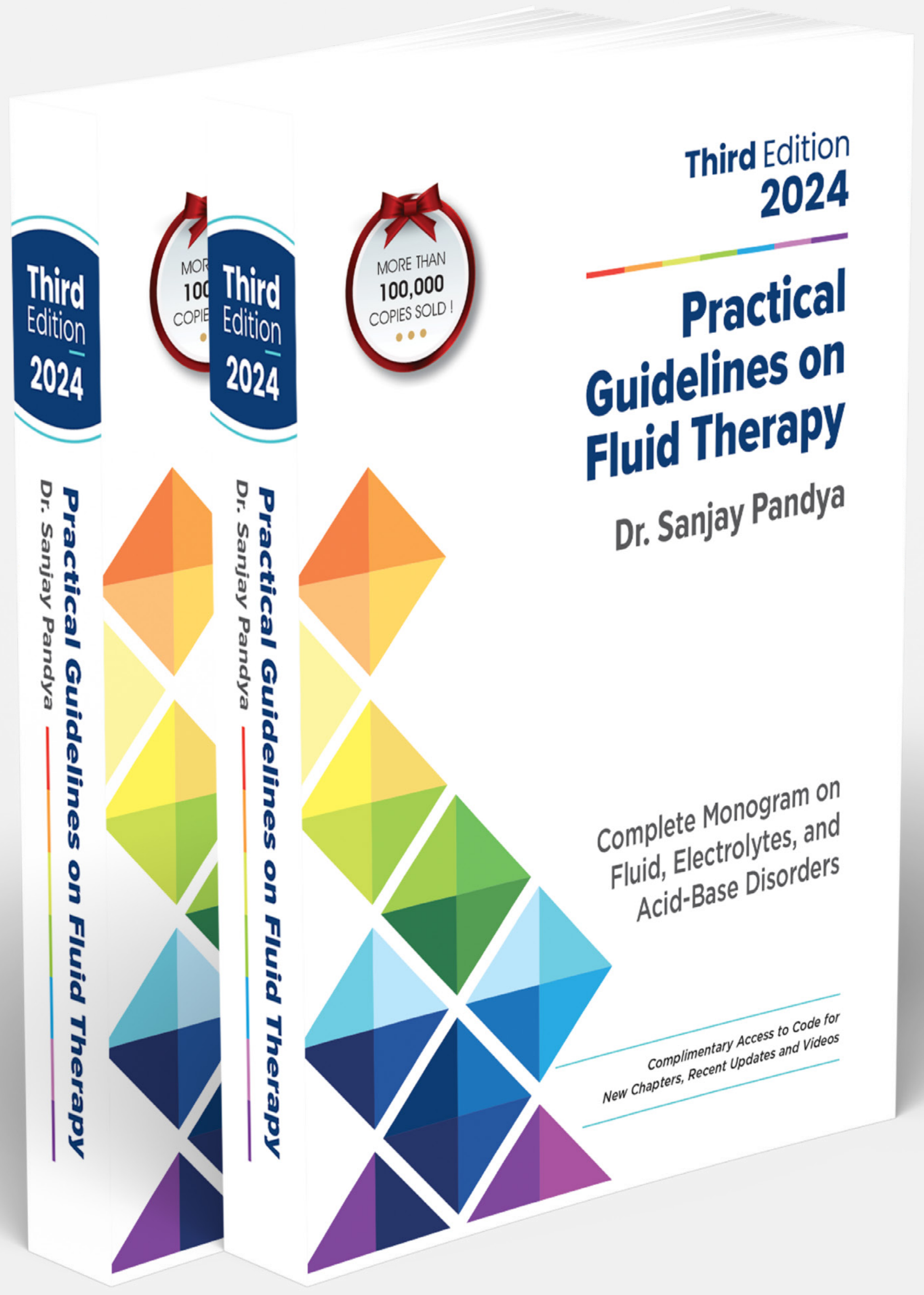
Chapter 31:

Metabolic Acidosis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Metabolic Acidosis

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Metabolic acidosis is a frequently encountered acid-base disorder in critical care patients, demanding meticulous attention and effective management due to its potential for serious consequences.

DEFINITION

It is characterized by a fall in plasma HCO_3 and a fall in pH (below 7.35). The $PaCO_2$ is reduced secondarily by hyperventilation, and this compensatory mechanism minimizes the fall in pH.

ETIOLOGY

Metabolic acidosis can result from the loss of HCO_3 via the gastrointestinal (GI) tract or kidneys, overproduction of endogenous nonvolatile acids, ingestion or infusion of acid or potential acids, and failure of H^+ excretion by the kidney.

Calculation of anion gap (AG) is extremely helpful in narrowing etiological diagnosis:

Anion Gap (AG)
$= Na^+ - (Cl^- + HCO_3)$
$= 12 \pm 2$ (Normal Value)

Metabolic acidosis can be classified into two groups based on the anion gap: high anion gap acidosis (e.g., lactic acidosis, ketoacidosis, ingested toxins, and acute or chronic renal impairment) and normal anion gap acidosis (e.g., diarrhea, renal tubular acidosis, or large volume saline administration). Table 31.1 summarizes the causes of metabolic acidosis classified based on the anion gap, their mechanisms of development, and how acidosis occurs in each cause.

The mnemonic "GOLDMARK" is helpful for remembering the causes of high anion gap metabolic acidosis (Table 31.2) [1].

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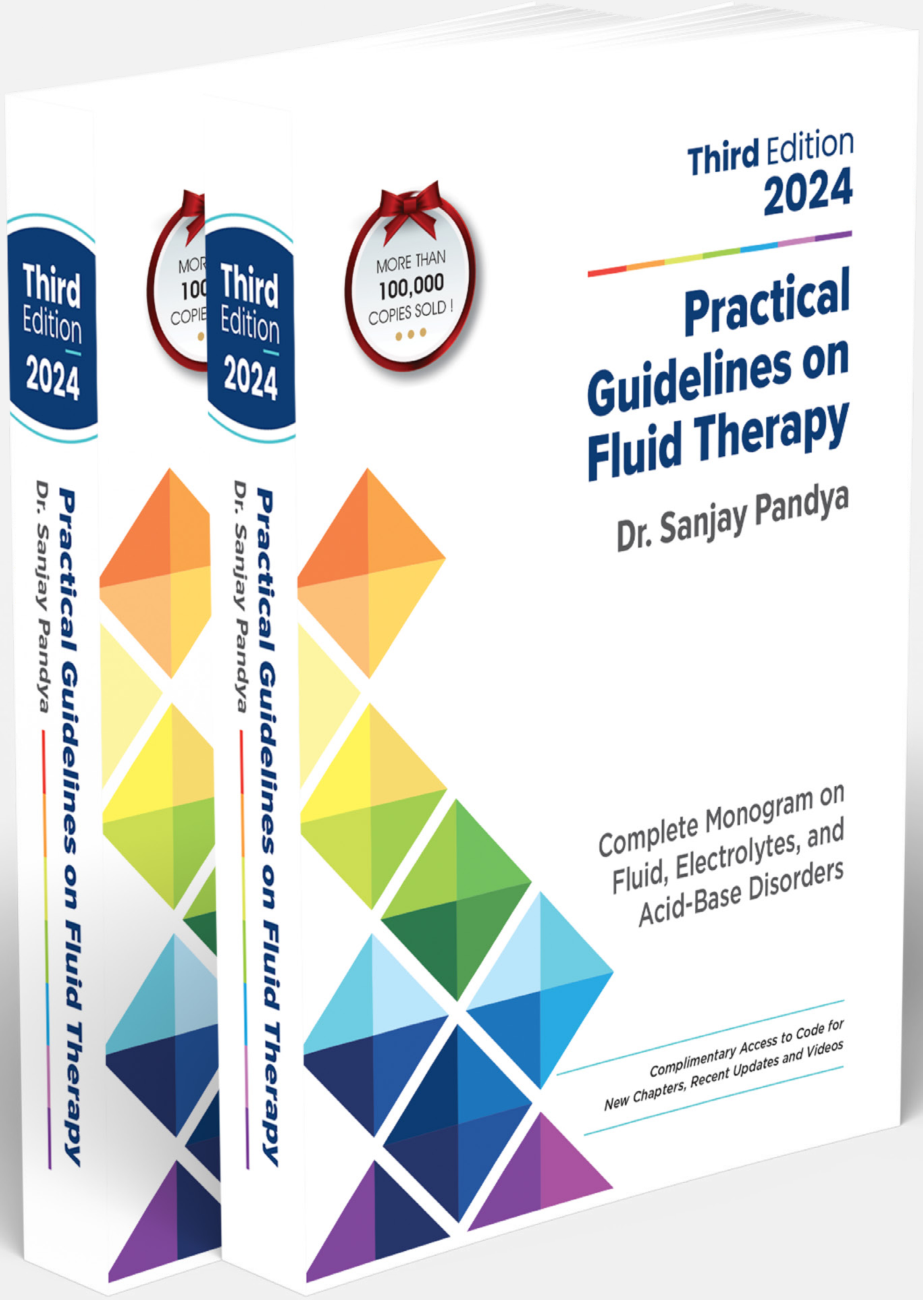
Chapter 32:

Metabolic Alkalosis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Metabolic alkalosis is the most common acid-base disorder, typically developing after hospitalization in critically ill patients, but it is not most frequently present upon admission, unlike metabolic acidosis [1, 2].

DEFINITION

Metabolic alkalosis is a primary acid-base disorder characterized by an increase in serum HCO_3 (>26 mEq/L), a high pH (>7.45), and a compensatory increase in $PaCO_2$ due to alveolar hypoventilation. Hypochloremia and hypokalemia are commonly encountered electrolyte imbalances in metabolic alkalosis.

Respiratory compensation: Hypoventilation, which occurs as a respiratory compensation in metabolic alkalosis, is a relatively slow process compared to the hyperventilation response that occurs in metabolic acidosis. Hypoventilation-induced hypoxia is a limiting factor for compensatory mechanisms in metabolic alkalosis because severe hypoxia (PO_2 <60 mm Hg) is a potent stimulus to increase alveolar ventilation, offsetting this protective respiratory response.

Comparison with chronic respiratory acidosis: Increased HCO_3 and increased $PaCO_2$ are also features of chronic respiratory acidosis, but the differentiating feature is a low pH.

PATHOGENESIS [3–5]

For a proper understanding of the pathogenesis of metabolic alkalosis, it is important to know the two distinct phases involved in sustaining metabolic alkalosis: 1. Generation of metabolic alkalosis and 2. Maintenance of metabolic alkalosis, as summarized in Table 32.1.

Generation of metabolic alkalosis

Mechanisms leading to the primary increase in plasma HCO_3 can involve one or more of the following:

- Gastrointestinal (GI) loss of hydrogen ion: Due to conditions like vomiting, nasogastric suction, or congenital chloride-losing diarrhea.

- Renal loss of hydrogen ion: It includes the use of diuretics, primary hyperaldosteronism, Bartter syndrome, and Gitelman syndrome.
- Exogenous HCO_3 load: Due to the administration of HCO_3, balanced crystalloids containing buffers, blood products containing citrate as an anticoagulant, and the development of milk-alkali syndrome.

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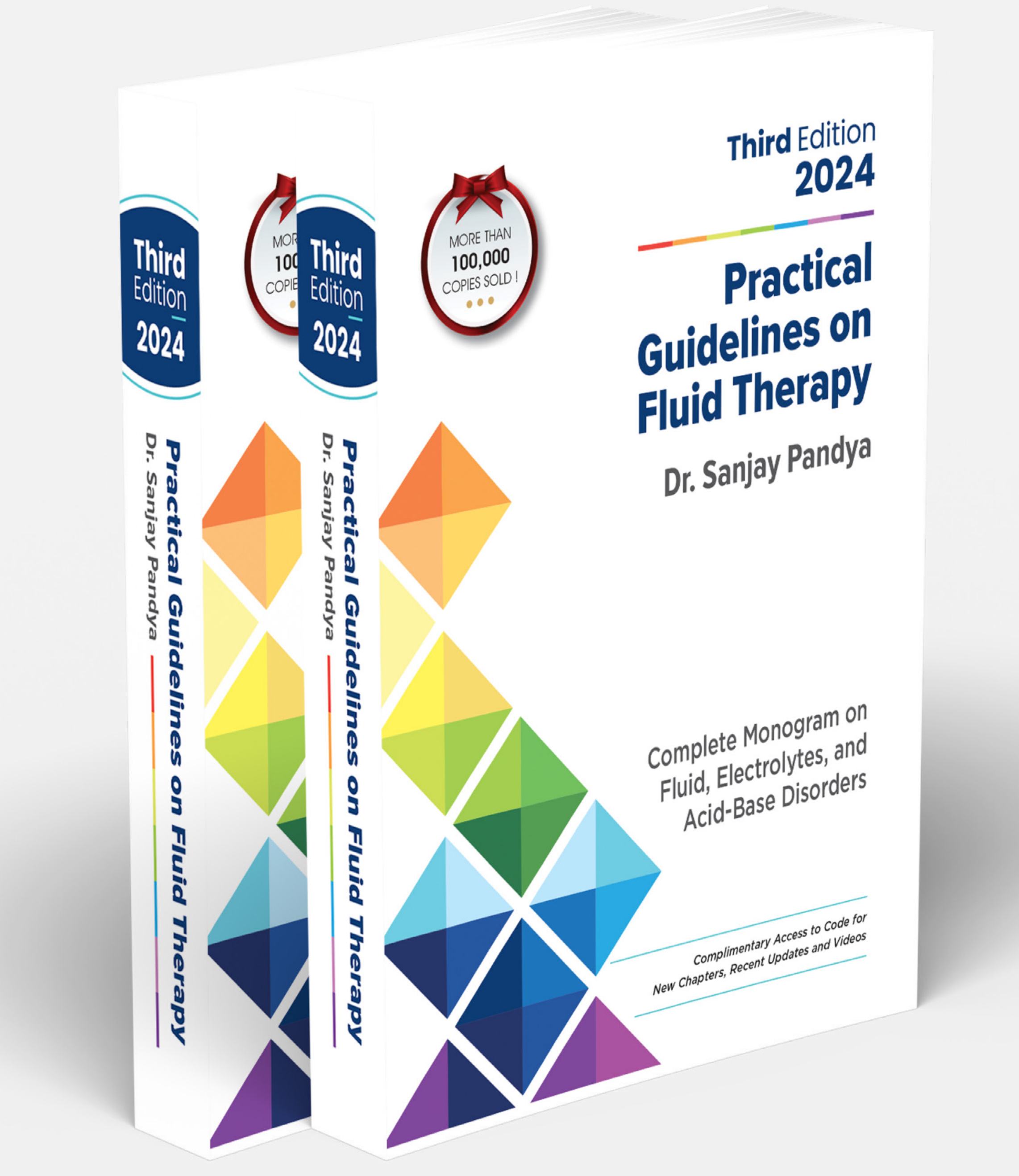
Chapter 33:
Respiratory Acid-Base Disorders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Respiratory Acid–Base Disorders

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Respiratory acidosis and respiratory alkalosis are the two primary respiratory acid-base disorders commonly encountered in clinical practice, both resulting from primary changes in pCO_2 due to various disorders.

RESPIRATORY ACIDOSIS

DEFINITION AND BASIC UNDERSTANDING

Respiratory acidosis, also known as primary hypercapnia, is a clinical disorder characterized by a primary elevation in the $PaCO_2$ (>45 mmHg) leading to a reduction in pH (<7.35) and variable compensatory increase in the plasma HCO_3 concentration.

Respiratory acidosis occurs when the effective alveolar ventilation (CO_2 excretion by the lung) fails to keep pace with the rate of CO_2 production. Acute respiratory acidosis occurs rapidly within <48 hours, while chronic respiratory acidosis develops slowly over days to weeks (>48 hours).

Renal compensation

Respiratory acidosis leads to renal compensation through increased urinary H^+ secretion, resulting in acidic urine. This gradual process leads to a rise in plasma HCO_3 levels, mitigating acidosis. Because renal compensation is a slow process, the compensatory increase in HCO_3 is small in acute respiratory acidosis. In contrast, in chronic respiratory acidosis, the compensatory rise in HCO_3 is more substantial over time due to robust and prolonged renal compensation.

Acute respiratory acidosis: Every 10 mm of Hg rise in $PaCO_2$ causes 1 mEq/L rise in HCO_3 and 0.1 fall in pH.

Chronic respiratory acidosis: Every 10 mm Hg rise in $PaCO_2$ causes a 4 mEq/L rise in HCO_3 and a 0.03 fall in pH.

Serum HCO_3 usually does not exceed 38 mEq/L due to compensation. If HCO_3 is >38 mEq/L, think of concomitant metabolic alkalosis.

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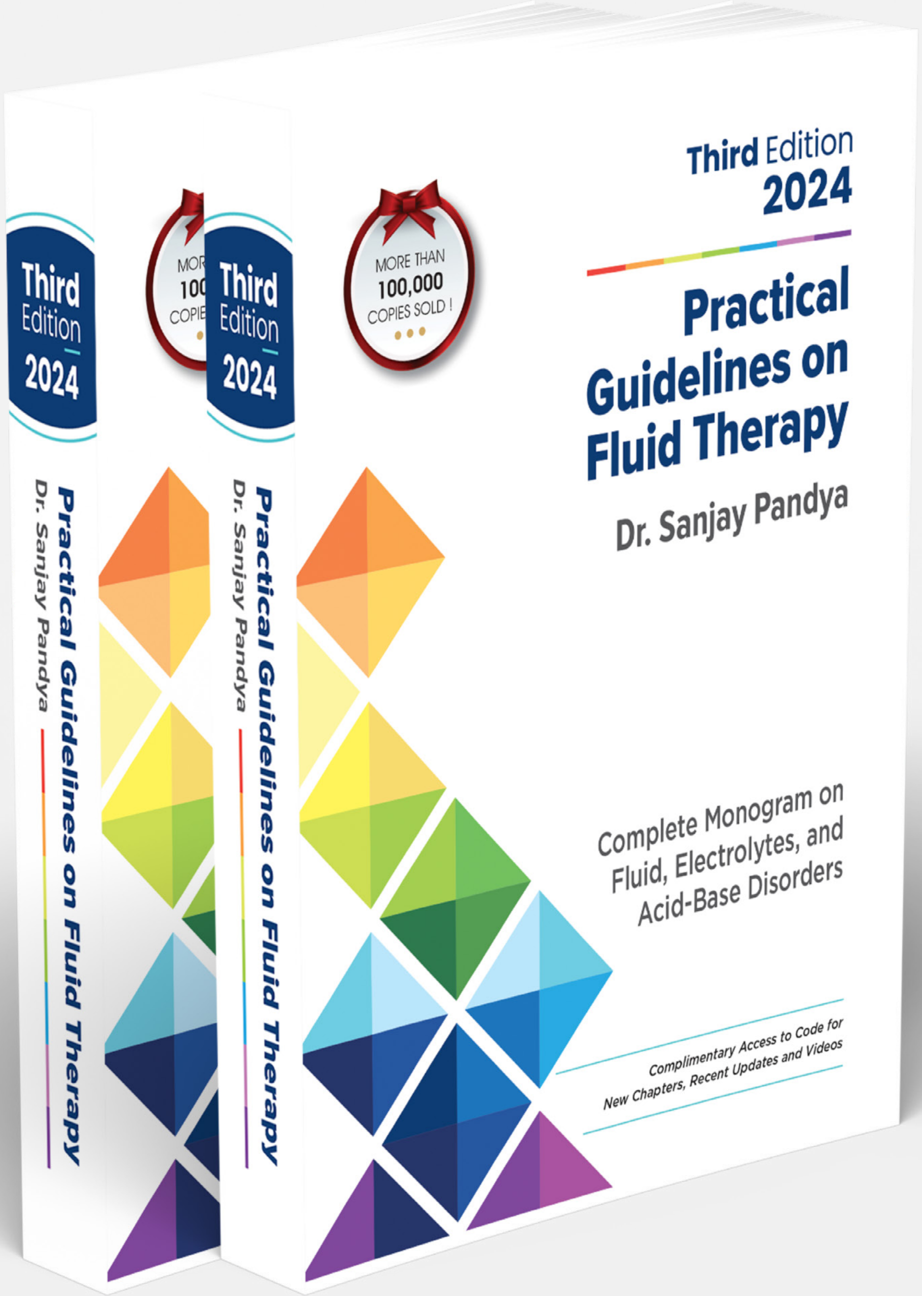
Chapter 34:

Gastrointestinal Losses and Upper GI Bleeding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Loss of gastrointestinal (GI) secretions and hematemesis are frequently encountered problems in clinical practice. Several gastrointestinal disorders lead to loss of GI secretions causing electrolytes and acid-base disturbances. The composition of gastrointestinal secretions and potential disturbances due to their losses are summarized in Table 34.1 [1–3], which will help plan its management.

The most common disorders, vomiting, diarrhea, and hematemesis, will be discussed.

VOMITING

Vomiting or nasogastric suction is a common problem in clinical practice causing loss of fluid and electrolytes. Therefore, it is necessary to understand the basic pathophysiology of hypovolemia and electrolytes and acid-base abnormalities due to upper GI losses and the proper selection of IV fluids to correct it.

FLUID AND ELECTROLYTE ABNORMALITIES

It is important to understand the fluid and electrolyte abnormalities that commonly occur due to vomiting.

Gastric juice contains approximately: Sodium (Na^+) 20–60 mEq/L, chloride (Cl^-) 140 mEq/L, potassium (K^+) 14 mEq/L, and hydrogen ions (H^+) 60–80 mEq/L [2].

So, vomiting (or nasogastric-NG suction) leads to hypokalemic, hypochloremic metabolic alkalosis with hypovolemia. Due to the loss of HCl containing gastric juice, the first abnormalities usually occur in vomiting are hypochloremia with metabolic alkalosis, and hypokalemia occurs subsequently. The pathogenesis of these abnormalities is summarized below (Figure 34.1).

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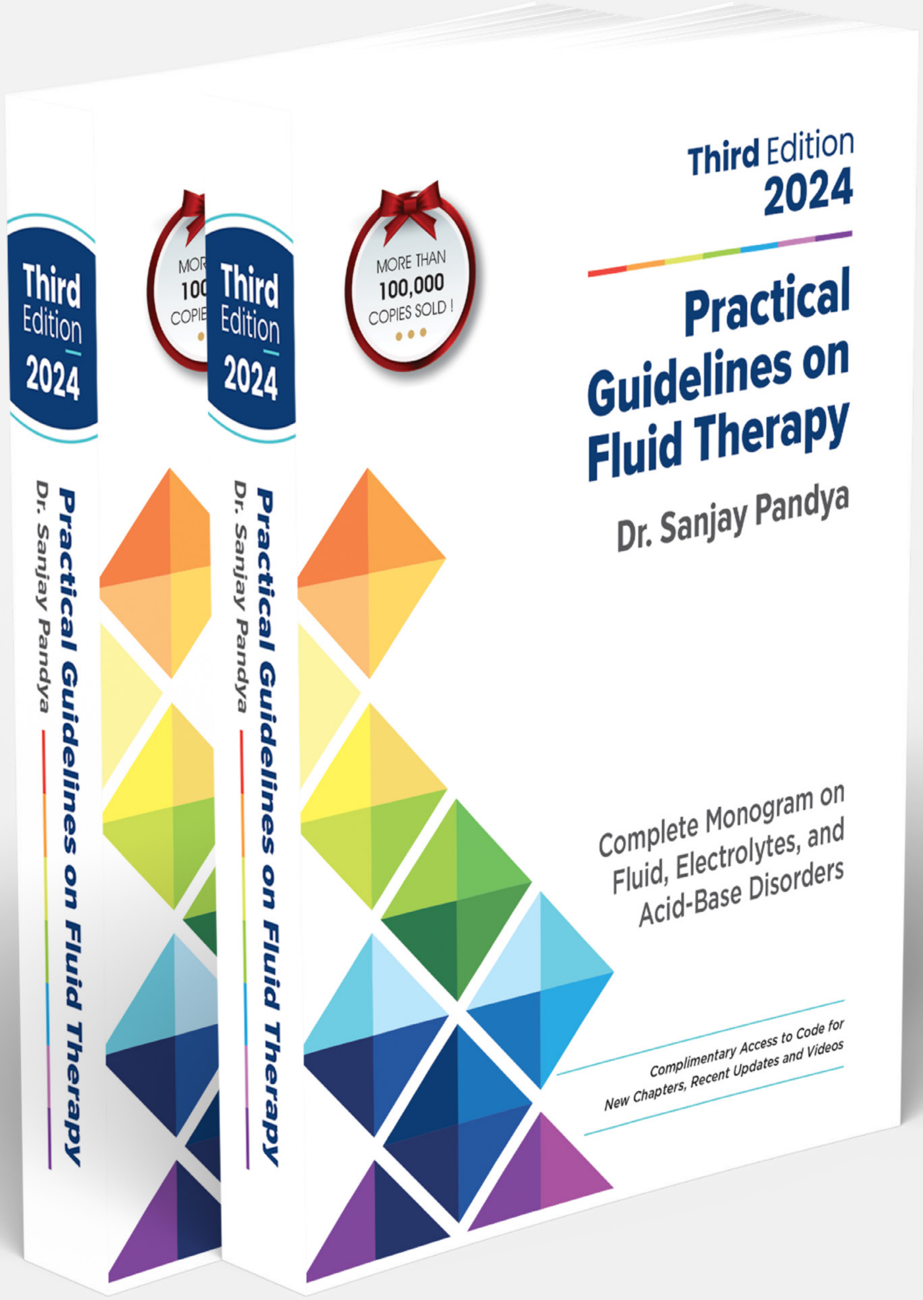
Chapter 35:

Ascites in Cirrhosis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The term ascites is defined as a pathologic fluid accumulation in the peritoneal cavity. The most common cause of ascites is decompensated cirrhosis which accounts for about 80% of the cases.

In patients with cirrhosis, ascites is the most common complication, which suggests the progression of diseases from a compensated to a decompensated stage [1]. About 60% of patients with compensated cirrhosis develop ascites within 10 years of its diagnosis [2]. Development of ascites in cirrhotic patients carries a poor prognosis as the five-year survival rate is significantly low in decompensated cirrhosis with ascites compared with compensated cirrhosis (about 30% vs. 80%) [1, 3].

Refractory ascites (RA) is defined as ascites that cannot be mobilized or recurs after large volume paracentesis (LVP) despite dietary sodium restriction and diuretic therapy. Refractory ascites is one of the most serious signs of the decompensated stage in liver cirrhosis which is associated with poor survival [4].

PATHOPHYSIOLOGY

In cirrhosis of the liver, the development of ascites is determined by four major factors: portal hypertension, splanchnic vasodilatation, renal sodium and water retention, and hypoalbuminemia.

A. **Portal hypertension:** The development of intrahepatic portal hypertension plays a crucial role in ascites formation. The normal value of portal pressure (pressure gradient between the hepatic and portal vein) is approximately <5 mm Hg. However, a portal pressure of usually >12 mmHg is required for ascites to develop. Without elevated portal pressure, ascites or edema do not occur.

   Portal hypertension occurs in liver cirrhosis because of both increased resistance to portal blood flow (increase in intrahepatic resistance due to distortion of the hepatic vascular architecture) and increased portal venous inflow (due to splanchnic vasodilatation). This increased portal hypertension increases hydrostatic pressure within the hepatic sinusoids, causing excessive fluid transudation into the peritoneal space, leading to ascites.

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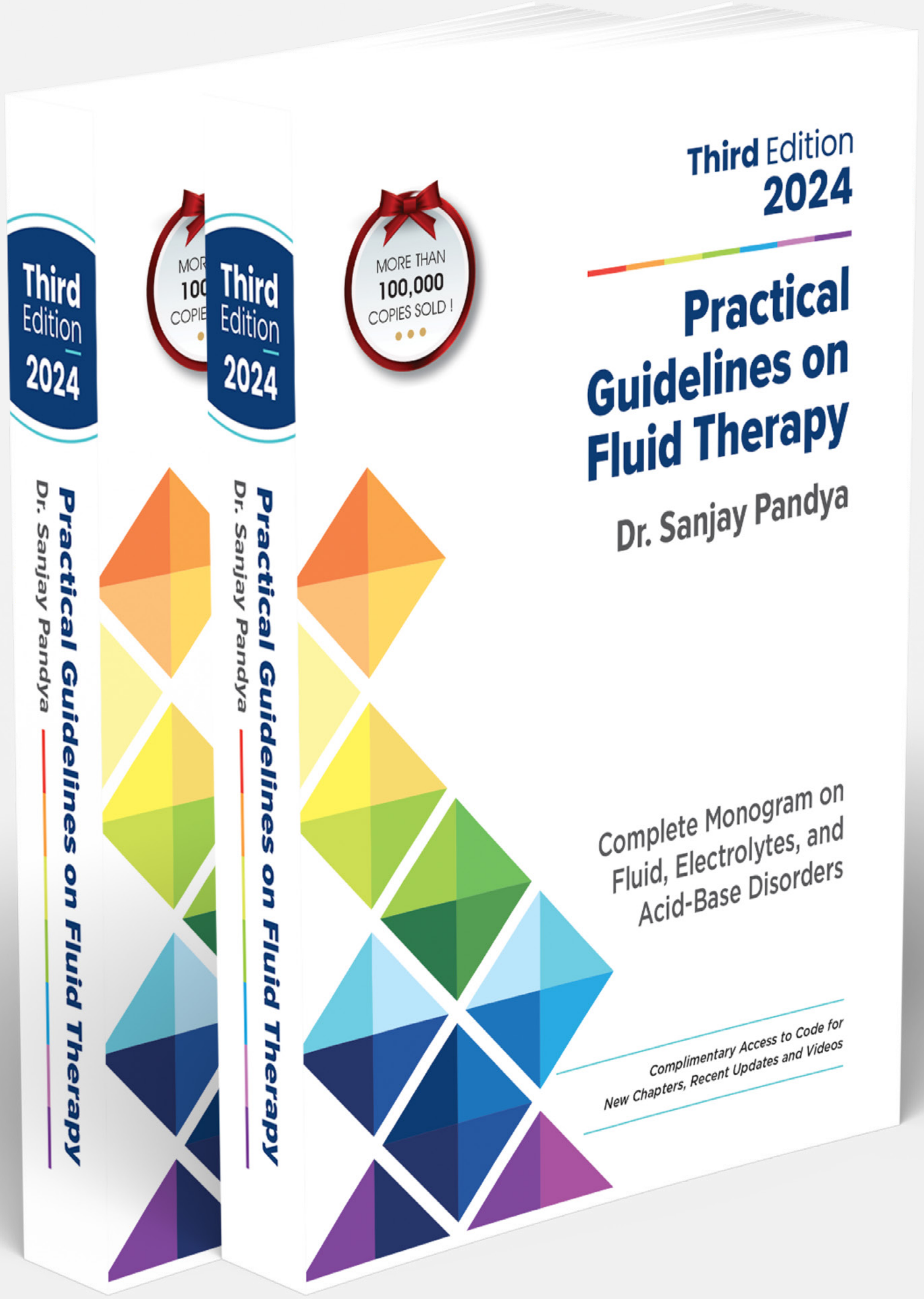
Chapter 36:

Hepatic Encephalopathy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Hepatic encephalopathy (HE) is a potentially reversible condition characterized by a spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma, which occurs as one of the many complications of decompensated liver disease or portosystemic shunting [1]. About 30 to 45% of patients with cirrhosis develop overt hepatic encephalopathy [2], which is associated with significant morbidity, mortality, high healthcare cost, and a huge burden on patients and their caregivers [3, 4].

PATHOPHYSIOLOGY

The pathophysiology of HE is poorly understood, it is often multifactorial, and different abnormalities may be present at the same time, leading to the development of HE [5].

The various pathogenetic mechanisms proposed in the development of HE are [5, 6]:

- Neurotoxins (Ammonia, benzodiazepines, benzodiazepine-like compounds such as gamma-aminobutyric acid, and manganese deposition within the basal ganglia).
- Alteration in neurotransmission due to increased GABA - neurotransmitters and serotonin activity in HE.
- False neurotransmitters such as tyramine, octopamine, and beta-phenylethanolamines may compete with the normal catecholamine neurotransmitters.
- Altered brain energy due to impaired hepatic gluconeogenesis in the terminal stages of liver failure.
- The systemic inflammatory response may exacerbate the harmful effects of hyperammonaemia on the brain [7].
- Alterations of the blood-brain barrier contribute to an increased influx of varieties of neurotoxic substances into the brain, which may contribute to HE.

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Chapter 37:
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Kidney failure is the most frequent organ failure in patients with acute or chronic liver disease, with a frequency of 20–50% in hospitalized cirrhotic patients [1–3].

Hepatorenal syndrome (HRS) is a life-threatening complication and one of many causes of acute kidney injury in patients with acute or chronic liver disease. HRS frequently occurs in hospitalized patients and is associated with a high mortality rate (about 32 to 37%) [4–6], readmission rate (about 23%) [5], hospital and health care costs [6, 7], and longer stay in hospital [4].

The most common precipitating factors of HRS are gastrointestinal bleeding, large volume paracentesis, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), spontaneous bacterial peritonitis, and other infections [5, 8].

DEFINITIONS AND TYPES OF HEPATORENAL SYNDROME

Hepatorenal syndrome is a specific cause of acute kidney injury (AKI) frequently encountered in advanced cirrhosis characterized by rapidly progressive renal failure, which occurs without apparent pathologic abnormalities in the kidneys [9].

Hepatorenal syndrome is traditionally classified into Type 1 and Type 2 HRS based on the severity of diseases reflected by the rapidity of decline in kidney function [10]. Type 1 (HRS-1) is a serious form of AKI that occurs in advanced cirrhosis with ascites.

Type 1 HRS is characterized by a rapid and progressive reduction in renal function (a 2-fold increase of serum creatinine to at least 2.5 mg/dL or a decrease of creatinine clearance by 50% to less than 20 mL/min within 2 weeks) [11], and has a poor prognosis (median survival only 8 to 12 weeks) [12]. Type 2 HRS is a less severe form of kidney function impairment that is slowly progressive and clinically characterized by ascites resistant to diuretics [11] and has a median survival of about 6 months [12].

The traditional classification of HRS-1 and HRS-2 has recently been reclassified (Type 1 HRS renamed as HRS-acute kidney injury (HRS-AKI), and HRS-2 renamed as HRS-NAKI (that is, non-AKI) [13–15]. Diagnostic features of HRS-AKI as recommendations by the International Club of Ascites (2019) are summarized in Table 37.1 [13].

PATHOGENESIS

The pathogenesis of HRS is multifactorial, complex, and poorly understood. However, two major mechanisms that interact and contribute to the development of HRS-AKI are the combination of hemodynamic abnormalities and systemic inflammation [3].

Table 37.1 Diagnostic criteria of HRS-AKI

1. Presence of cirrhosis and ascites
2. Presence of AKI (increase in serum creatinine >0.3 mg/dL within 48 hours, or >50% increase in serum creatinine from baseline in 3 months)
3. Lack of improvement of serum creatinine (decrease of creatinine ≤0.3 mg/dL of baseline) after at least 48 hr of diuretic withdrawal and volume expansion with albumin (1 gm/kg body weight/day for 2 d)
4. Absence of shock (septic, cardiogenic, distributive)
5. Exclusion of current or prior treatment with nephrotoxic drugs
6. Absence of proteinuria ≥500 mg/day, microhematuria, or structural abnormalities on ultrasonography

A. Hemodynamic abnormalities: The "splanchnic arterial vasodilation theory" is the main hypothesis in the pathophysiology of HRS [16]. Essential components of the pathogenesis of neurohormonal cascade in HRS are:

- **Vasodilatation:** In portal hypertension, increased intrahepatic vascular tone promotes the release of vasodilatory substances like nitric oxide and prostaglandins, which cause arterial vasodilatation in the splanchnic and systemic circulation.
- **Activation of vasoconstrictors:** Systemic and splanchnic vasodilatation reduces effective arterial blood volume and systemic arterial pressure, which triggers the carotid and aortic arch baroreceptors and activates three powerful vasoconstrictor systems (renin-angiotensin-aldosterone system, vasopressin release, and activation of the sympathetic nervous system).
- **Renal vasoconstriction:** Activation of vasoconstrictor systems increases arterial pressure and kidney vasoconstriction. In advanced stages of cirrhosis, synthesis of vasodilator factors is more pronounced with further vasodilatation of systemic and splanchnic and resultant worsening of hypotension [17]. Vasoconstrictor systems are further activated [18] to combat severe hypotension and achieve optimal arterial pressure, which is compatible with life. As renal circulation is very sensitive to the vasoconstrictive effects of these vasoconstrictors, it causes a marked reduction in renal perfusion and the development of HRS-AKI [19].
- **Cardiac dysfunction:** In cirrhotic patients with systemic vasodilation, cardiac output increases initially. But

with the progression of liver disease, cardiac output decreases, further reducing impaired renal blood flow and contributing to the development of hepatorenal syndrome [20, 21].

B. Systemic inflammation: According to this new theory, in portal hypertension, gut permeability increases, causing bacterial translocation from the gut to mesenteric lymph nodes, which triggers a systemic inflammatory response with the release of pro-inflammatory cytokine [18]. Three different mechanisms by which systemic inflammation causes organ dysfunction, and failure are [22–24]: (1) Nitric oxide production in splanchnic arterioles due to systemic inflammation accentuates the preexisting splanchnic vasodilation and stimulates endogenous vasoconstrictor systems causing renal hypoperfusion; (2) Activation of immune cells resulting in tissue damage; and (3) Metabolic alterations.

DIAGNOSIS

In patients with cirrhosis, renal dysfunction can occur due to HRS and many other causes for the development of AKI in cirrhotic patients, such as hypovolemia (gastrointestinal [GI] bleeding, use of diuretics or GI losses), medications (drug-induced or contrast-induced nephropathy), infections, intrinsic renal disease, and obstructive uropathy [25]. In cirrhotic patients with HRS, multiple causes that can potentially lead to AKI can coexist and overlap [26].

While evaluating AKI in patients with liver disease, it is important to remember that hepatorenal syndrome is the cause of AKI in about 15–43% [27, 28], AKI frequently occurs due to hypovolemia in 27–50% of all cases, and acute tubular necrosis (ATN) in about 14–35%.

As hepatorenal syndrome (HRS-AKI) is a diagnosis of exclusion, it is essential to exclude other potential causes of kidney injury in patients with liver disease [15, 18]. So detailed history, clinical assessment, laboratory assessments, and abdominal imaging should be performed to exclude different causes of AKI, such as prerenal AKI (hypovolemia), acute tubular necrosis (hypovolemic shock, infection, or nephrotoxic agents), and other causes (abdominal compartment syndrome, glomerulonephritis, acute interstitial nephritis, and obstructive uropathy) [29, 30]. Differentiating ATN and HRS-AKI may be difficult, and in such patients, the role of urinary biomarkers is promising and may prove helpful [31, 32].

PREVENTION

As HRS carries a poor prognosis, it is better to prevent than treat it. Measures to prevent HRS are:

- Avoid using nephrotoxic drugs (such as NSAIDs, aminoglycosides, amphotericin, ACE-I, angiotensin receptor blockers, or radiographic dye), and use diuretics and laxatives judiciously.
- Early detection and prompt treatment of coexisting infections and antibiotic prophylaxis in patients with increased risk of spontaneous bacterial peritonitis are effective measures to prevent AKI-HRS [28].
- Correct intravascular volume depletion, which may occur due to excessive diuretic use, diarrhea due to lactulose, variceal bleeding, and large volume paracentesis without albumin administration).
- IV albumin infusion: In patients with spontaneous bacterial peritonitis, the IV administration of albumin reduces the risk of both kidney function impairment and mortality [33–35].
- In patients with spontaneous bacterial peritonitis, albumin is started

together with antibiotics. The recommended dose of IV albumin to prevent HRS is 1.5 gm/kg within 6 hours of detection of infection (on the first day) and a second dose of 1 gm/kg after 48 hours of the first dose (on the third day).

- During large volume paracentesis, replacing 6–8 gm of albumin for every liter of ascites removed reduces the risk of HRS-AKI [14, 30, 36, 37].
- Antibiotics prophylaxis: In patients with advanced cirrhosis, administration of oral norfloxacin (or alternative trimethoprim-sulfamethoxazole if norfloxacin is unavailable) decreases the one-year probability of spontaneous bacterial peritonitis, delays the development of HRS, and improves survival [38]. Rifaximin also reduced the incidence of HRS-AKI in cirrhotic patients [39, 40].
- Early diagnosis and prompt management of gastrointestinal bleeding.
- Pentoxifylline: Due to its protective effect against oxidative renal cell injury, pentoxifylline (1200 mg/day) is found to reduce the risk of HRS-AKI in alcoholic hepatitis and may be an effective prophylaxis [41–44]. However, larger studies are needed to validate the efficacy [45, 46].
- As HRS is a common complication in acute alcohol hepatitis, early detection and treatment of alcoholic hepatitis, alcohol abstinence, and proper nutritional supplementation are essential [47].

MANAGEMENT

HRS requires early and aggressive therapy because, besides all therapeutic advances, the outcome of HRS is poor.

The goals of management of hepatorenal syndrome are:

- Identify and treat reversible factors.
- To correct hypovolemia and avoid volume overload.
- To achieve a higher mean arterial blood pressure (rise in MAP ≥10–15 mmHg from baseline) is the most effective approach for better perfusion of the kidneys [29, 48, 49].
- Reversal of hemodynamic disturbances and acute kidney injury.
- To stabilize the patient, provide renal replacement therapy if necessary, and prolong survival until candidates undergo liver transplantation.

Three primary treatment options for managing HRS are general measures, pharmacological therapy, and non-pharmacological therapy.

A. General measures

- Meticulous evaluation to diagnose underlying precipitating factors and their early treatment.
- Volume expansion. The first step in managing AKI in cirrhosis is volume expansion (with crystalloids or intravenous albumin). As prerenal AKI is the most common cause of renal failure in cirrhotic patients, it is essential to correct hypovolemia immediately by replacing fluids, considering the cause and severity of the fluid loss [14, 18, 50]. Normal saline infusion is preferred to correct hypovolemia due to vomiting or the excess dose of diuretics. Blood or blood products effectively correct hypovolemia and anemia due to gastrointestinal bleeding. The reversal of AKI in 48 hours with volume expansion favors prerenal AKI [50].
- Assessing the volume status of cirrhotic patients can be challenging due to the complexity of the condition. At times it can be challenging to correct hypovolemia optimally in these patients because they may

have intravascular volume depletion despite the presence of ascites or peripheral edema. Additionally, over-infusing fluids can worsen existing conditions such as ascites, pleural effusion, heart failure, or respiratory failure [51].

- To determine the best approach for volume assessment and fluid management, a careful history, detailed clinical examination, laboratory tests, X-ray-based imaging, and point-of-care ultrasound should be used [52].
- Stop β-blockers in patients with low or borderline blood pressure [14]. Discontinue nephrotoxic drugs (as discussed in prevention).
- Stop diuretics and avoid the temptation to use diuretics to increase urine output in severe AKI in HRS [14]. Diuretic therapy in HRS can lead to volume depletion and further reduction of effective circulating volume, which can aggravate renal hypoperfusion and may trigger or worsen HRS [53, 54]. In addition, it is essential to discontinue spironolactone in HRS as it carries the risk of life-threatening hyperkalemia.
- As spontaneous bacterial peritonitis is a main triggering factor of AKI-HRS, its prompt treatment with albumin and antibiotics helps in preventing AKI-HRS [28, 33, 34]. But the administration of albumin is not recommended in patients of HRS with non-spontaneous bacterial peritonitis infections [55, 56].
- Always search for the presence of electrolyte disorders (such as hyponatremia, hyperkalemia, hypokalemia, etc.) or acid-base disorders (such as respiratory alkalosis, metabolic alkalosis, and metabolic acidosis) and treat them [51].
- Etiology-driven management of AKI.
- Measure vitals, urine output, fluid balance, and daily weight and closely monitor patients.

B. Pharmacological therapy

Combined therapy with albumin and a vasopressor is recommended as the first line of treatment for HRS-AKI and should be started as soon as possible [14, 18, 30, 57].

1. Albumin

In cirrhotic patients with AKI, administering albumin is important for both diagnostic and therapeutic purposes [18, 58].

It is essential to differentiate AKI-HRS from prerenal AKI because AKI occurs due to prerenal AKI in about half of patients with AKI in cirrhosis.

Renal recovery within 48 hours after administration of albumin (along with removing risk factors and discontinuing diuretics) favors the diagnosis of prerenal AKI, and failure in improvement in renal function suggests the diagnosis of AKI-HRS [15].

IV Albumin is recommended for volume resuscitation in prerenal AKI regardless of the etiology or severity of prerenal azotemia [52].

Effects: Albumin infusion increases oncotic pressure, effectively expands circulating volume, improves hemodynamics and cardiac output, increases renal perfusion, and enhances renal recovery.

In addition to volume expanding effects in HRS, other benefits of albumin proposed in current literature are [37, 58, 59] antioxidant and anti-inflammatory effects [60, 61], positive cardiac inotropic effects [62], improvement in the autoregulation of renal perfusion [63], preservation of the integrity of endothelial glycocalyx [64], and stabilization of endothelial function [65].

Dose: Recommended dose of albumin is 1 gm/kg/d (up to 100 gm/d) for two consecutive days, preferably given in divided doses (e.g., 25 gm every 6 hourly) [13, 14]. Subsequently, the dose may decrease to 20–40 gm daily. However, as per the recent ATTIRE trial (2021), tailoring albumin therapy to raise serum albumin to 3.0 gm/dL or more is not beneficial in reducing infection, kidney dysfunction, or death [66].

Combination therapy: It is important to remember that instead of albumin alone, combination therapy of albumin with vasoconstrictor therapy is more effective [67–70]. Therefore all guidelines recommend albumin with vasoconstrictor, the adjunct therapy for HRS-AKI [3, 14, 30, 57]. This combination therapy significantly improves renal function in HRS and reduces mortality compared with no treatment or albumin alone [15, 71, 72].

Duration of treatment: Albumin plus vasoconstrictor therapy should be continued until serum creatinine reduces to a value within 0.3 mg of the baseline value of serum creatinine [15].

Combination therapy is discontinued within 14 days if patients do not respond or respond partially [15].

Adverse effect: The major concern of albumin infusion in HRS is the significant risk of volume overload, especially pulmonary edema [66, 70].

So, before administration, it is essential to assess volume status and avoid albumin infusion in patients with volume overload.

As albumin increases preload and terlipressin increases afterload, the combined treatment carries the risk of precipitation of pulmonary edema [29].

2. Vasoconstrictors

Administration of IV albumin, combined with vasoconstrictors such as IV terlipressin, noradrenaline, or oral midodrine plus octreotide initiated as soon as the diagnosis of HRS is suspected. The combination therapy helps in the reversal of hemodynamic disturbances, restoration of effective circulating volume, and improvement in renal perfusion.

a. Terlipressin

According to international guidelines, terlipressin, a synthetic vasopressin analog, is recommended as the first and most preferred vasoconstrictor for managing HRS [14, 18, 25, 30, 57, 73, 74]. This is because it has been shown to improve renal function in 24–44% of patients in various studies [68–70, 75–79] and meta-analyses [69, 71, 72, 80–83], making it an effective treatment option for HRS. In addition, potent vasoconstrictor terlipressin is also found to reduce short-term mortality and hospital cost in various studies [71, 72, 81, 84, 85]. But the effect on mortality is controversial as survival benefits are lacking in other literature [69, 70, 76, 80].

Mechanism of action: Terlipressin has a high affinity for V1 receptors. V1 receptors are predominantly located in the splanchnic bed and systemic vascular smooth muscle, while V2 receptors are found more commonly in the kidney. Because of its selective effect, terlipressin causes splanchnic vessels and extrarenal vasoconstriction, which improves effective circulating volume and renal perfusion pressures.

Indications: In HRS, initiate terlipressin at early stages of AKI (i.e., serum creatinine >1.5 mg/dL), as there is a higher likelihood of a positive response to treatment when initiated at an earlier stage. However, avoid using terlipressin in milder forms of HRS-AKI (i.e., serum creatinine <1.5 mg/dL) as they are typically benign and potentially reversible with fluid expansion alone. Terlipressin should also be avoided in patients with advanced renal dysfunction (i.e., serum creatinine >5.0 mg/dL or higher).

Dose: Initial dosage of terlipressin in HRS is 1–2 mg/12 h by continuous IV infusion or 0.5–1.0 mg/4–6 h by IV boluses, and the dose is progressively increased as per need [14]. In the absence of response, the dose of continuous IV terlipressin infusion should be increased stepwise from 2 mg/day to a maximum of 12 mg/d according to the change in urine output and serum creatinine [74, 86]. One ampoule (8.5 ml solution) contains 1 mg terlipressin acetate.

Route: Administration of terlipressin by continuous IV infusion is preferred over IV boluses because infusion is better tolerated, and the requirement of effective doses is lower [87].

Poor response: Response to terlipressin is poor in HRS-AKI patients with higher total serum bilirubin [88], higher serum creatinine [89], underlying chronic kidney disease (CKD) with significant structural kidney injury, presence of severe bacterial infections [90], and failure to achieve an increase in the mean arterial pressure and cardiac output [73].

Contraindications: As terlipressin causes extrarenal vasoconstriction, it is usually avoided in HRS patients with coronary artery disease, cerebral or peripheral vascular diseases, cardiac arrhythmias, asthma, chronic obstructive pulmonary disease, and elderly patients [91].

Adverse effects: Common adverse effects of terlipressin are abdominal pain, nausea, diarrhea (due to gastrointestinal smooth muscle spasm), coronary or peripheral vascular ischemic complications, and respiratory adverse events. Serious side effects like dyspnea and respiratory distress occur because of terlipressin-induced pulmonary vasoconstriction and cardiac overload because of increased afterload due to terlipressin and preload due to albumin [74, 92].

Measures suggested to reduce respiratory adverse events of terlipressin are judicious use of albumin and careful attention to respiratory distress, monitoring pulse oximetry, and frequent chest radiographs or point of care ultrasound [93].

Terlipressin was introduced first time in the year 1990 and was widely used worldwide subsequently. But due to respiratory adverse events [70] and the lack of mortality benefits [94], it was not approved by the FDA and therefore was unavailable. However, recently, in September 2022, the US FDA approved the use of terlipressin for the treatment of hepatorenal syndrome in adults [95].

b. Norepinephrine (Noradrenaline)

In a country like the USA, where terlipressin was unavailable till recently (September 2022), norepinephrine (plus albumin) was a preferred agent and considered a first-line treatment for HRS [52]. Early studies and meta-analyses have shown equal effectiveness of terlipressin plus albumin and norepinephrine plus albumin in reversing HRS [96–101], but in a recent study, terlipressin plus albumin was associated with a higher HRS reversal rate in patients with acute on chronic liver failure [102].

The advantages of norepinephrine are that it is significantly cheaper than terlipressin and is widely available with fewer side effects [78, 96, 100, 101, 103]. In addition, physicians use norepinephrine routinely and are very familiar with its use because it is the most standard drug for augmenting sepsis circulation.

But the requirements of the central venous catheter for its administration and the need for ICU or close monitoring for potential adverse effects such as arrhythmia and ischemia may offset the cost-benefit of this drug [103–105].

Mechanism of action: Alpha-adrenergic agonist norepinephrine by nonselective systemic vasoconstriction improves the mean arterial pressure and renal perfusion in HRS.

Dose: The dose of norepinephrine varies from 0.5 to 3 mg/h in HRS. Norepinephrine is usually started at an initial dose of 1 mg/hour by continuous infusion and is gradually increased to maintain the mean arterial blood pressure to ensure renal perfusion [106].

c. Midodrine and octreotide

In the USA, until now, the combination of midodrine and octreotide is routinely used to treat HRS-1 in general wards because terlipressin was not available in the USA, and norepinephrine cannot be administered outside of the intensive care unit [52]. But as compared to terlipressin and norepinephrine, the combination of midodrine and octreotide has shown low rates of renal recovery in HRS [72, 107, 108].

Therefore, midodrine and octreotide having much lower efficacy than terlipressin, are not preferred in ICU patients and are used in general wards only when terlipressin is unavailable [14, 30].

The combination of midodrine and octreotide plus albumin is the most effective therapy for increasing serum sodium in dilutional hyponatremia associated with HRS [83].

Midodrine is an orally available alpha-adrenergic agonist which causes systemic vasoconstriction and improves renal perfusion. Midodrine is usually started at a dose of 5–7.5 mg thrice daily orally, which can be increased maximum up to 15 mg three times daily as needed [109]. Synthetic somatostatin octreotide is potent splanchnic vasoconstriction which is given either as a continuous infusion (usual initial dose 50 mcg/h) or subcutaneously (usual dose 100–200 mcg/8 h) [109]. The combination of octreotide and midodrine is beneficial in HRS, but midodrine as a monotherapy does not improve renal function.

The selection of vasoconstrictors with albumin in hepatorenal syndrome based on treatment setup (in the intensive care unit or ward) is summarized in Table 37.2.

C. Non-pharmacological therapy

When patients do not respond to the above pharmacological measures, treatment options are dialysis, transjugular intrahepatic portosystemic shunt (TIPS), liver transplantation, or simultaneous liver-kidney transplantation.

1. Renal replacement therapy (RRT)

The use of RRT in patients with HRS is controversial [110–112]. HRS patients with failure of medical treatment but the possibility of improvement in kidney or liver function or patients who are eligible for liver transplantation are usually offered RRT [52]. Common indications of RRT in HRS-AKI are worsening renal function, electrolyte disturbances, or increasing volume overload besides optimum vasoconstrictor therapy [30].

2. Transjugular intrahepatic portosystemic shunt

TIPS may be used as a salvage therapy when medical management fails. When the intrahepatic stent is connected between the portal vein and the hepatic vein, it redirects portal blood into the systemic circulation, which decompresses the portal system and increases systemic

<table>
<tr><th colspan="5">Table 37.2 Vasoconstrictor with albumin in hepatorenal syndrome</th></tr>
<tr><td colspan="5">**Albumin**
To all patients (expands intravascular volume)</td></tr>
<tr><td colspan="5">**Choice of vasoconstrictors**</td></tr>
<tr><td></td><td>Setup</td><td>Firstline drugs</td><td>Class</td><td>Route</td></tr>
<tr><td rowspan="2">Terlipressin available</td><td>ICU</td><td rowspan="2">Terlipressin</td><td rowspan="2">Vasopressin analog</td><td rowspan="2">IV</td></tr>
<tr><td>Wards</td></tr>
<tr><td rowspan="2">Terlipressin not available</td><td>ICU</td><td>Norepinephrine</td><td>Alpha agonist</td><td>IV</td></tr>
<tr><td>Wards</td><td>Midodrine and octreotide</td><td>Alpha agonist
Somatostatin analog</td><td>Oral and SQ</td></tr>
<tr><td colspan="5">Duration of therapy: About 1–2 weeks</td></tr>
<tr><td colspan="5">Goal: To raise mean arterial pressure by 10–15 mm of Hg, reduction of serum creatinine <1.5 mg/dL</td></tr>
</table>

venous return leading to the return of more blood to the heart, causing increased cardiac output and improvement in arterial and renal perfusion. In a recent meta-analysis, it was found that TIPS can improve serum creatinine levels, urine volume, and urinary sodium excretion [113].

However, TIPS is not routinely recommended in patients with AKI-HRS because: (1) In clinical practice, its use is very limited (contraindicated in HRS with severe liver failure or severe hepatic encephalopathy) [14]; (2) It is associated with complications such as procedure-related bleeding, worsening of liver function, or development of hepatic encephalopathy [114]; and (3) Its role of in HRS is not precisely defined [115] and data supporting its use are insufficient [30].

3. Liver transplantation

Liver transplantation is the only curative treatment and therapy of choice for both types of HRS. But unfortunately, this most effective modality is available to a small fraction of the affected patients, and many patients die before a donor liver can be obtained.

4. Simultaneous liver-kidney transplantation (SLKT)

SLKT is usually recommended in patients with HRS-AKI when kidney function is not expected to recover post-liver transplantation (e.g., AKI associated with dialysis ≥6 weeks and glomerular filtration rate [GFR] ≤25 mL/min for more than 6 weeks or presence of underlying advanced CKD or CKD requiring dialysis) [116, 117].

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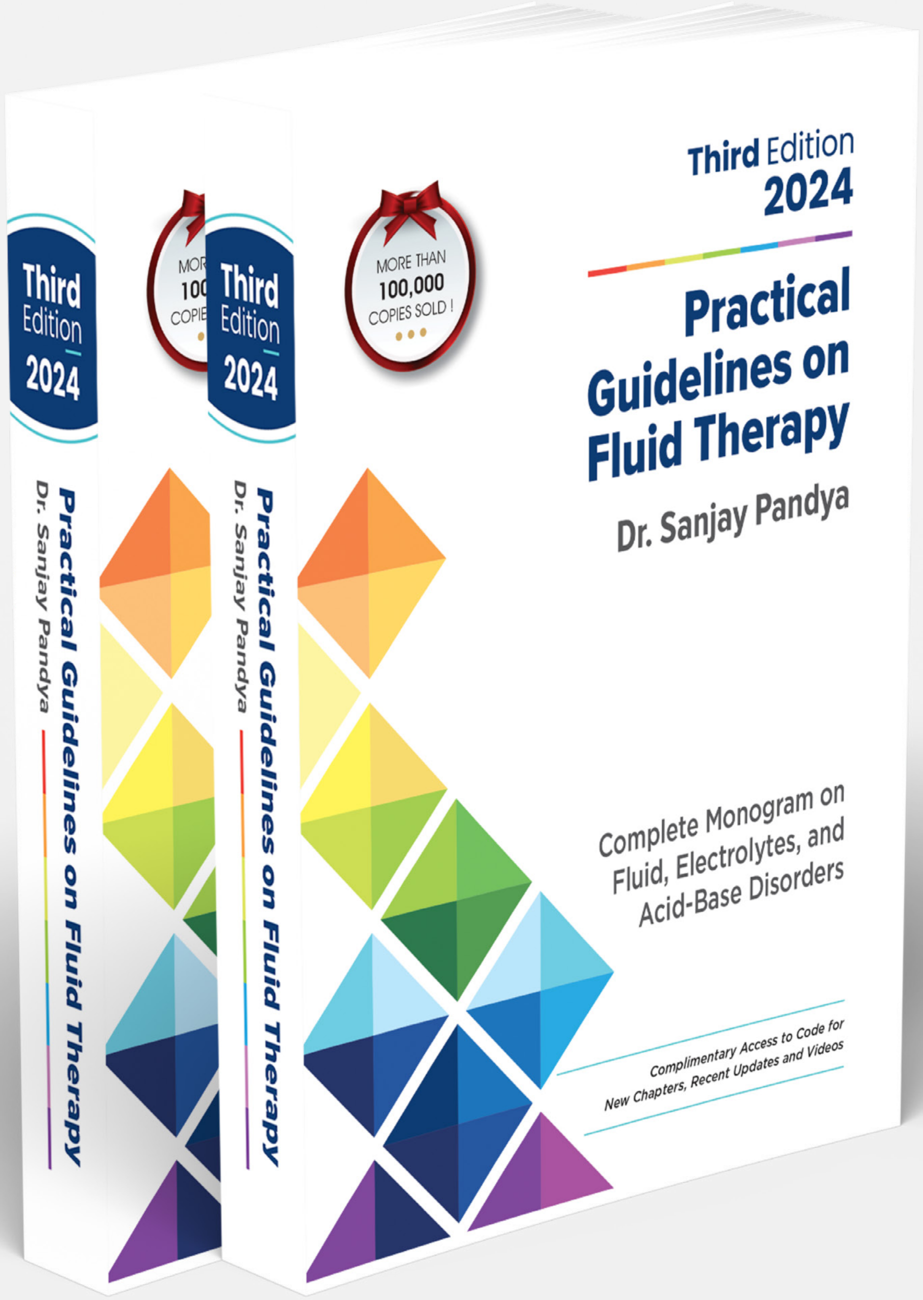
Chapter 38:

Acute Pancreatitis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Acute Pancreatitis

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Acute pancreatitis (AP) is a common gastrointestinal tract disease that occurs due to cellular injury and inflammation of the pancreas and is characterized by the abrupt onset of deep epigastric pain and elevated levels of lipase or amylase levels in the blood [1, 2]. Acute pancreatitis is increasing globally; it is one of the most common gastrointestinal causes of hospitalization in the United States and is associated with significant morbidity, mortality, and substantial health care cost [3–5].

CAUSES

The most common causes of acute pancreatitis are gallstones (about 42%) and chronic alcohol use (about 21%), while less frequent causes are hypertriglyceridemia, post-endoscopic retrograde cholangiopancreatography, hypercalcemia, trauma, infection, and idiopathic [6, 7].

DIAGNOSIS

The diagnosis of acute pancreatitis requires at least two of the following three criteria: (1) Typical abdominal pain (acute onset severe, persistent, epigastric, and left upper quadrant abdominal pain); (2) Threefold elevation in pancreatic enzymes activity (serum lipase and serum amylase); and (3) Imaging (computerized tomography [CT], magnetic resonance imaging [MRI], ultrasound) findings that are consistent with acute pancreatitis [8].

CLASSIFICATION

Based on pathological changes, onset, and severity, acute pancreatitis is classified in Table 38.1 [3, 8–16].

MANAGEMENT

Treatment of acute pancreatitis should be individualized depending on the severity of the disease, causative etiology, presence of complications of severe acute pancreatitis, and coexisting disorders. Management of acute pancreatitis is divided into three broad categories:

A. Initial medical management
B. Endoscopy therapy
C. Surgical therapy

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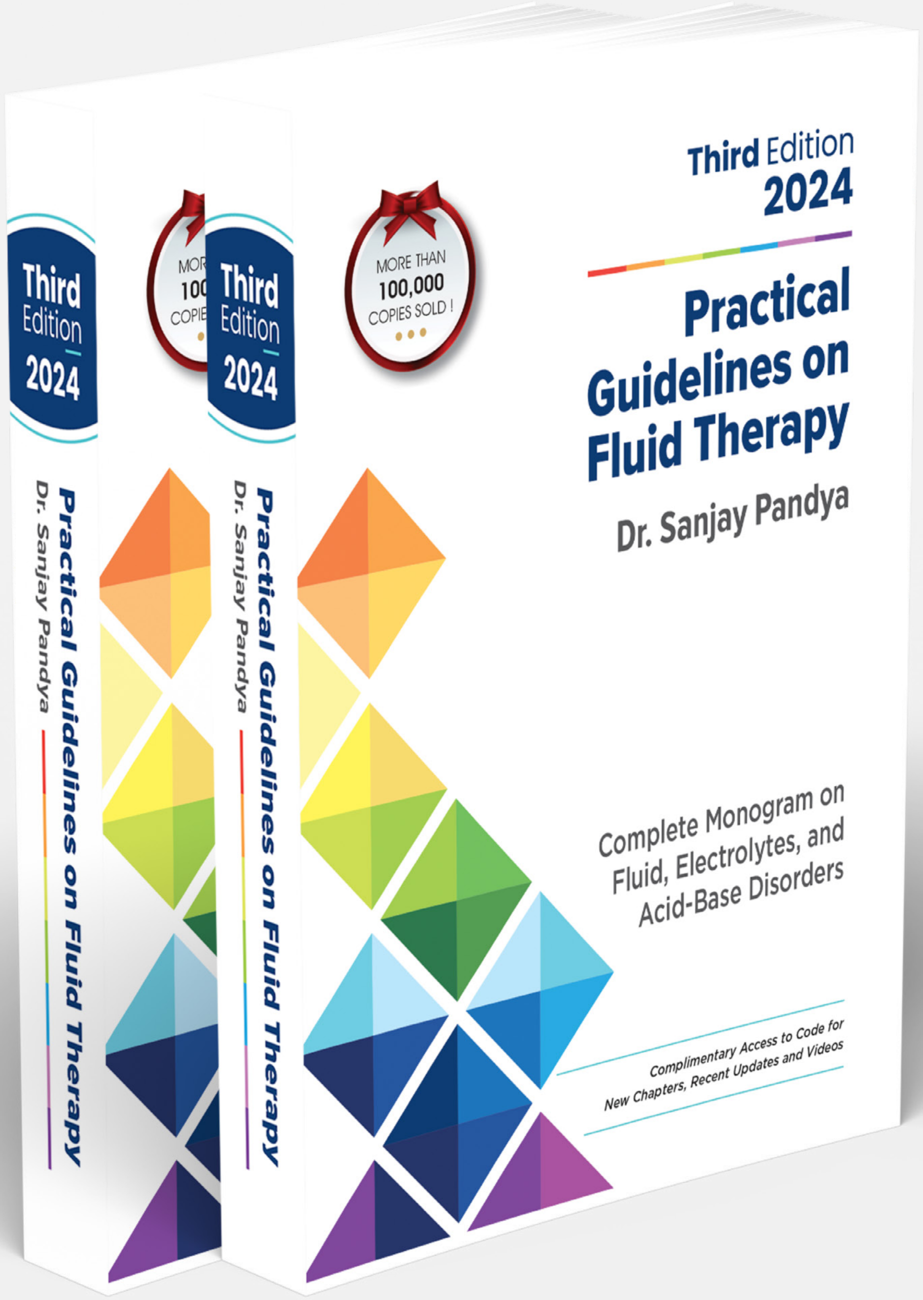
Chapter 39:

Fluid Therapy in Bronchial Asthma, ARDS, and in Mechanical Ventilation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Fluid Therapy in Bronchial Asthma, ARDS, and in Mechanical Ventilation

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Fluid therapy in common respiratory disorders such as acute respiratory distress syndrome, bronchial asthma, and patients receiving mechanical ventilation is discussed.

BRONCHIAL ASTHMA

In patients with bronchial asthma, important aspects of fluid therapy, electrolyte disorders, and acid-base disorders are discussed.

A. Fluid therapy

Adequate hydration protects the lung epithelium and helps in promoting effective mucociliary clearance [1, 2]. In dehydration, cough is significantly more prevalent, even in healthy individuals [3]. Poor oral intake during illness, increased work of breathing due to airway obstruction, increased insensible fluid losses due to hyperventilation, cold sweat during an asthma attack, and fluid loss due to associated fever all contribute to the loss of body water and sodium chloride during an asthma attack [4].

Proper hydration is essential because dehydration worsens respiratory symptoms and lung function in patients with bronchial asthma [5].

Dehydration carries problems such as:

1. Thickened secretions, which can lead to mucus plugging and airway obstruction.
2. Stimulates the production of inflammatory markers like histamine that leads to airway obstruction via smooth muscle contraction, bronchial secretion, and airway mucosal edema [6, 7].

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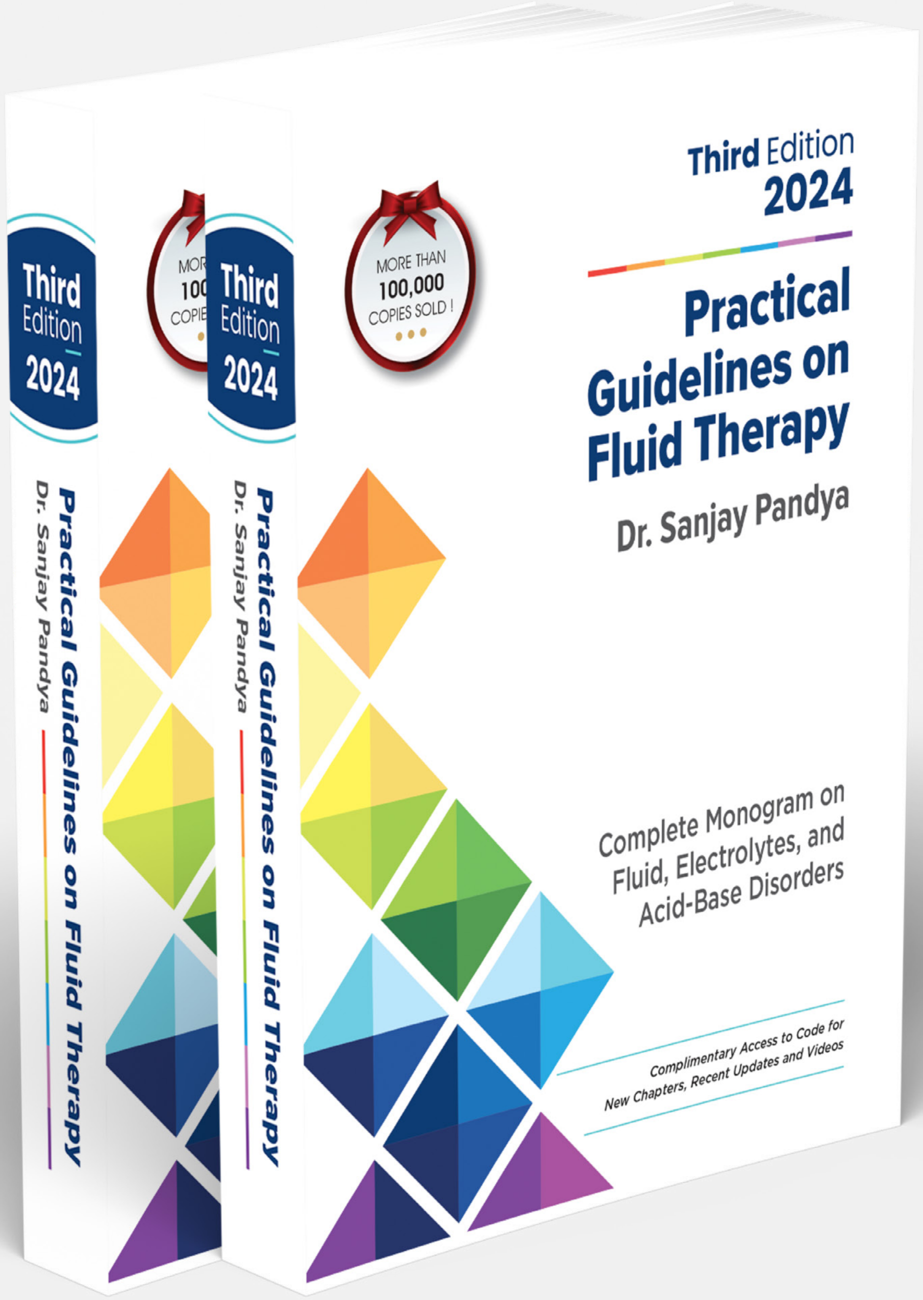
Chapter 40:

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State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Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

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Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are serious and potentially life-threatening metabolic complications of diabetes mellitus (DM). While DKA is a common hyperglycemic emergency with a low mortality rate, characterized by hyperglycemia and ketoacidosis, HHS, on the other hand, is less common, characterized by hyperglycemia and hyperosmolality without ketoacidosis, but has a high mortality rate.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis is a medical emergency that can be life-threatening if not treated promptly. DKA is one of the common complications of type-I diabetes mellitus (IDDM) associated with significant fluid and electrolyte imbalance.

DEFINITION

Diabetic ketoacidosis is characterized by the triad of [1, 2]:

1. Hyperglycemia: Blood glucose concentration of >200 mg/dL or 11.0 mmol/L.
2. Metabolic acidosis: Venous pH <7.3 and serum bicarbonate <18 mmol/L [1] (or 15 mmol/L [2]).
3. Ketonemia or ketonuria: Capillary ketones >3 mmol/L or urine ketones ++ ("moderate or large").

If a facility to measure blood beta-hydroxybutyrate (BOHB) concentration is available, it is a more precise and sensitive test to diagnose DKA [3].

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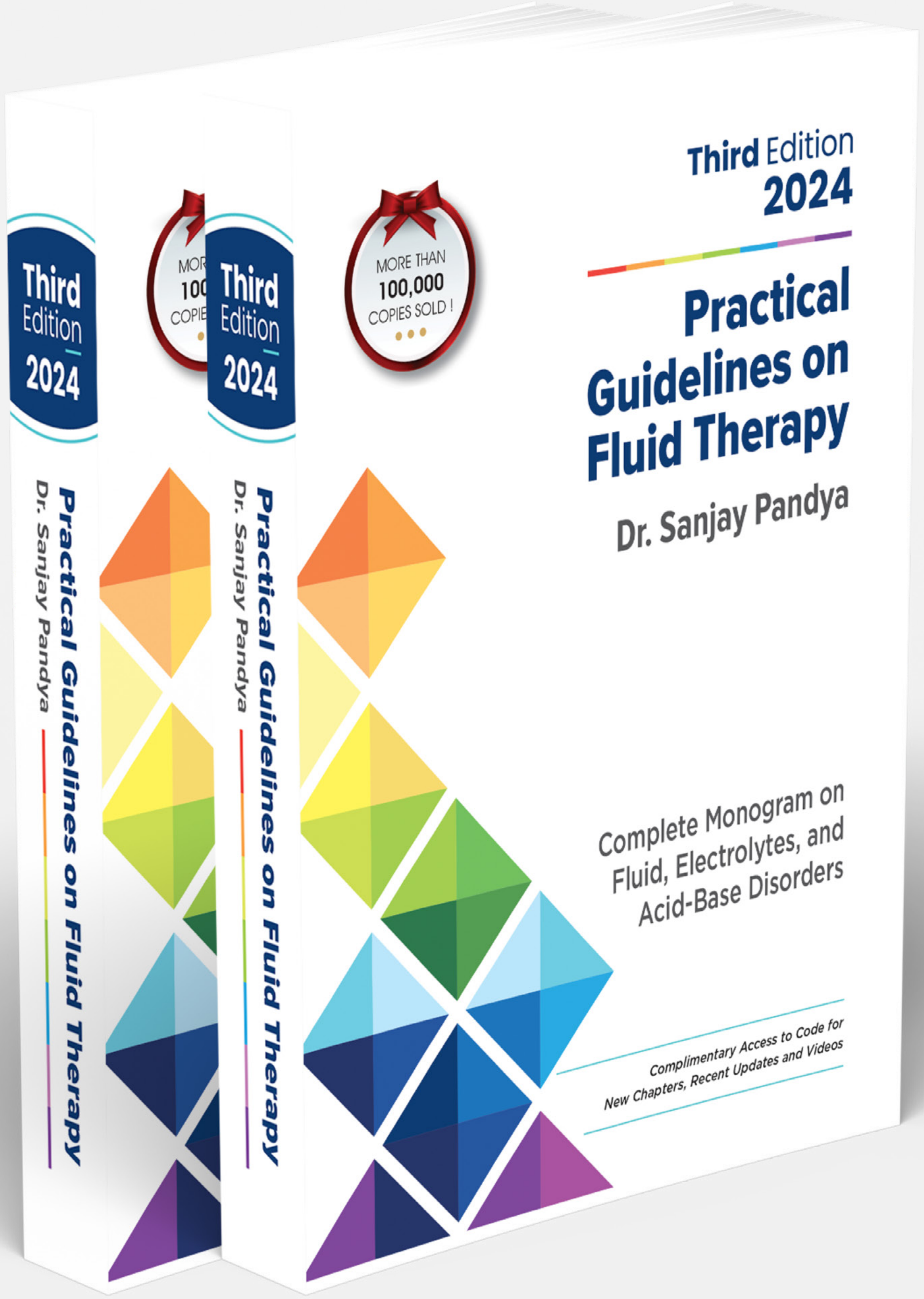
Chapter 41:
Neurological Disorders



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IMPORTANCE OF FLUID REPLACEMENT

Fluid replacement is of utmost importance in patients with traumatic brain injury (TBI) or those undergoing neurosurgery. These patients require the administration of intravenous solutions to achieve three important goals: (1) Achieve hemodynamic stability, (2) Improve cerebral perfusion and ensure adequate cerebral oxygenation to prevent brain damage, and (3) Prevent cerebral edema [1–3].

Aneurysmal subarachnoid hemorrhage (aSAH) patients are prone to volume contraction due to cerebral salt wasting, resulting in increased urine output. Therefore, they require fluid replacement. Furthermore, the combined effect of volume depletion and cerebral vasospasm resulting from aSAH increases the risk of cerebral ischemia and life-threatening ischemic strokes, leading to significant morbidity and mortality [4].

So, patients with aSAH require large volumes of sodium-rich IV fluids to correct hypovolemia, maintain euvolemia and normonatremia [5], and prevent the associated poor outcomes [6, 7].

SELECTION OF FLUIDS

To choose the ideal intravenous solution for neurological disorders, it is essential to understand the benefits and harmful effects associated with the solution's composition, tonicity, and type of buffer [3]. The 2018 ESICM consensus and clinical practice recommendations suggest using crystalloids as first-line resuscitation and preferred maintenance fluids and advise against using colloids in neurointensive care patients [8].

A. Normal saline: Preferred fluid

Isotonic solution normal saline (0.9% sodium chloride) is the most commonly used and preferred crystalloid for neurological patients [9, 10].

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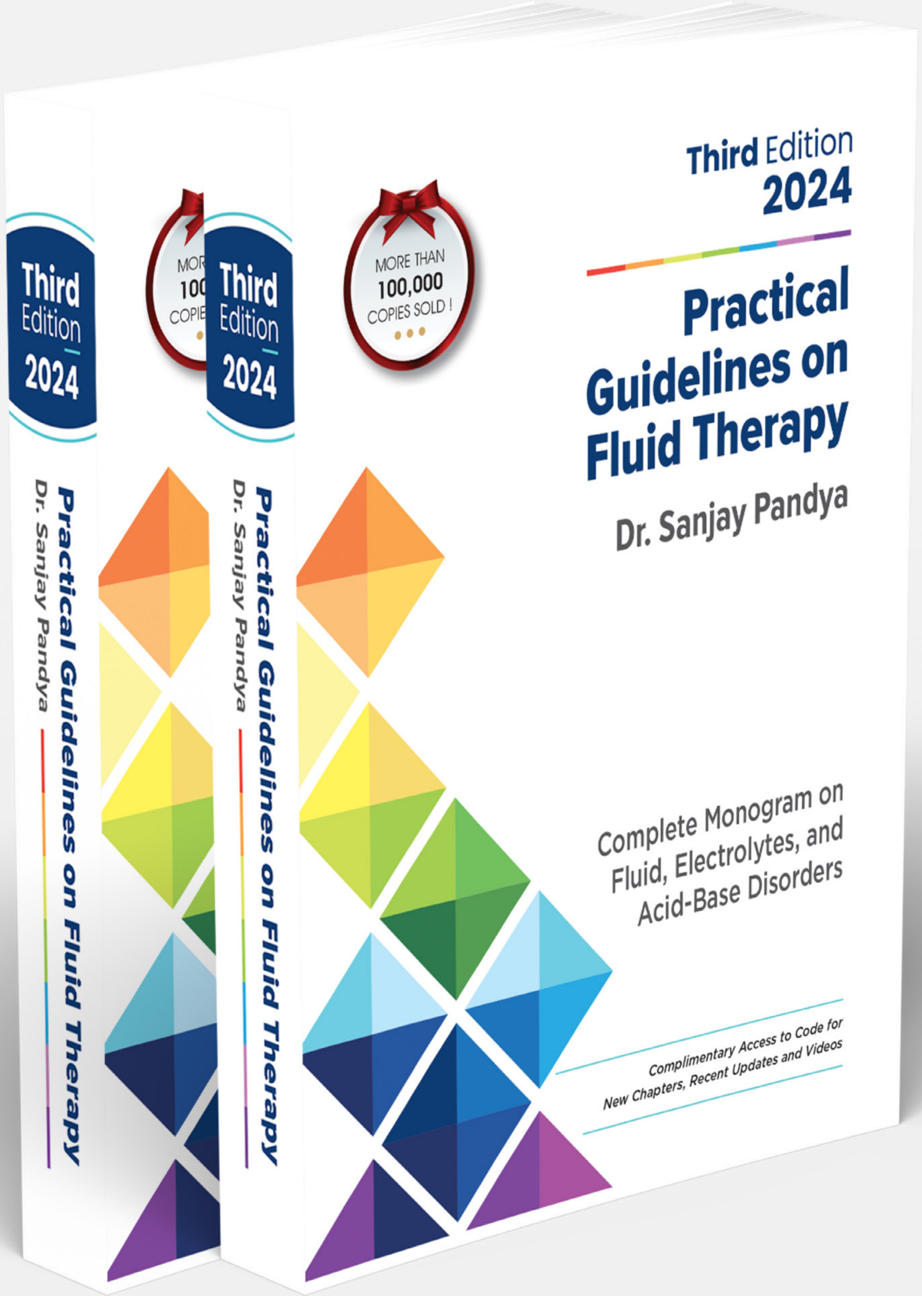
Chapter 42:

Preoperative Fluid Therapy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Fluid therapy in surgical patients is a critical part of perioperative care that involves the administration of fluids to maintain the patient’s hemodynamic stability, organ perfusion, and hydration status during and after surgery.

Timely administered intravenous fluid is vital and can be lifesaving in surgical patients. The type and amount of fluids administered depend on various factors, such as the patient's preoperative status, the extent of surgical trauma, the duration of surgery, and associated illnesses and comorbid conditions. Proper fluid management can help reduce complications after major surgery, decrease stay in the hospital, and improve patient outcomes [1].

Understanding the possible fluid and electrolyte imbalances in surgical patients and their proper management is important to achieve optimal outcomes after surgery.

NEED FOR SPECIAL CONSIDERATIONS

In surgical patients, several factors can modify the normal physiology of fluid and electrolyte balance in the body, which requires special consideration. Some important factors that need to be considered are:

- In surgical patients, the secretion of ACTH increases due to acute stress. This increased adrenocorticotropic hormone (ACTH) level stimulates the adrenal glands to secrete two hormones: a large amount of cortisol to fight acute stress and aldosterone, which results in sodium retention and urinary loss of potassium. Hypovolemia during major surgery also leads to increased aldosterone secretion. The increased aldosterone secretion for the first 2-3 postoperative days leads to increased sodium and water reabsorption.
- Postoperative pain and stress can cause an increase in antidiuretic hormone (ADH) secretion from the posterior pituitary gland during the first 2-3 postoperative days. By reducing urine output and increasing water reabsorption, ADH helps in the correction of hypotension in postoperative patients. It is important to remember that the amount of maintenance fluid required on the first

postoperative day is lower due to the increased ADH secretion.

- Fluid deficit resulting from preoperative oral fluid restriction (nothing by mouth-NPO) must be taken into account and replenished prior to or during the surgery to maintain proper hydration.

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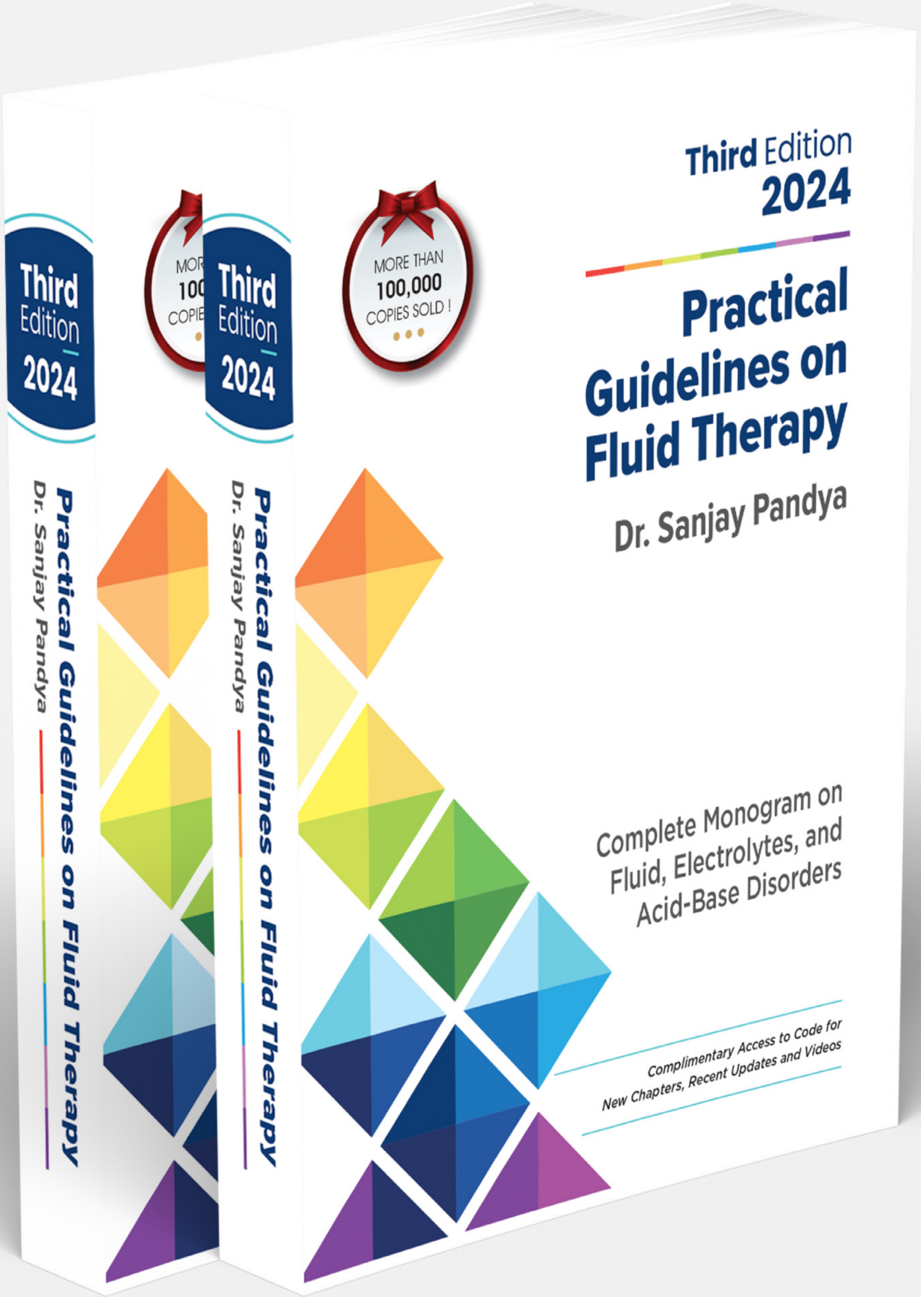
Chapter 43:

Intraoperative Fluid Therapy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INTRAVASCULAR VOLUME DISTURBANCES

Intraoperative hypovolemia and hypotension are common in high-risk prolonged surgeries, such as major abdominal or cardiac procedures, among vulnerable populations, including elderly patients and those with preexisting medical conditions, and are associated with high morbidity, risk of postoperative mortality, and adverse postoperative outcomes [1, 2].

Proper fluid therapy is an essential and critical component of intraoperative management. Its goal is to prevent and correct hypovolemia and hypotension while avoiding fluid overload. Fluid overload is harmful as it carries the risk of impaired tissue oxygenation, pulmonary edema, impaired wound healing, acute kidney injury (AKI), prolonged bowel dysfunction, and longer hospital stay in surgical patients [3, 4]. Adequate fluid therapy ensures proper tissue perfusion and oxygenation, which are crucial for maintaining optimal surgical outcomes.

To avoid hypovolemia and hypotension, along with appropriate fluid replacement, it is essential to diagnose and treat the underlying causes.

Causes of hypovolemia

Causes of intraoperative hypovolemia and hypotension include [5, 6]:

1. Surgical blood loss: This is a major cause of hypovolemia, and the volume of blood loss depends on several factors, including the type and duration of the surgery, as well as any preexisting or acquired defects in hemostasis. Trauma surgery is the most common cause of severe blood

loss. Concurrently, the use of anticoagulant therapies like warfarin, and antiplatelet agents such as clopidogrel, can further elevate the risk of bleeding during surgery.

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Postoperative Fluid Therapy

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Postoperative fluid therapy is crucial for managing patients' fluid needs, ensuring their physiological stability, maintaining hydration and tissue perfusion, restoring fluid balance, and supporting recovery during the postoperative period. The administration of fluid and electrolytes during the postoperative period depends on a thorough patient evaluation, and no single postoperative fluid regimen suits everyone [1].

THE GOAL OF FLUID THERAPY

The aim of postoperative fluid therapy is to keep the patient normovolemic, maintain an adequate circulating blood volume, optimize organ perfusion, promote wound healing, provide adequate calories to prevent catabolism and prevent complications such as hypovolemia, fluid overload, electrolyte imbalances, and acid-base disturbances.

In postoperative patients, the major principles of management of fluid balance are:

- To replace ongoing losses (hemorrhage, drainage, third space losses, and insensible losses)
- To provide maintenance requirements
- To correct preexisting deficits (preoperative and intraoperative losses)

CAUSES OF HYPOVOLEMIA

Hypovolemia and hypotension are common postoperative complications, and their important causes include:

- Bleeding: Intraoperative and postoperative blood loss.
- Fluid deficit: Inadequate correction of the preoperative starvation (nothing by mouth-NPO) deficit, utilization of "zero-balance" or "restrictive fluid strategy" to replace intraoperative losses, failure to adequately replace maintenance fluid requirements during prolonged surgeries, and ongoing fluid losses from the gastrointestinal tract (such as vomiting and diarrhea).

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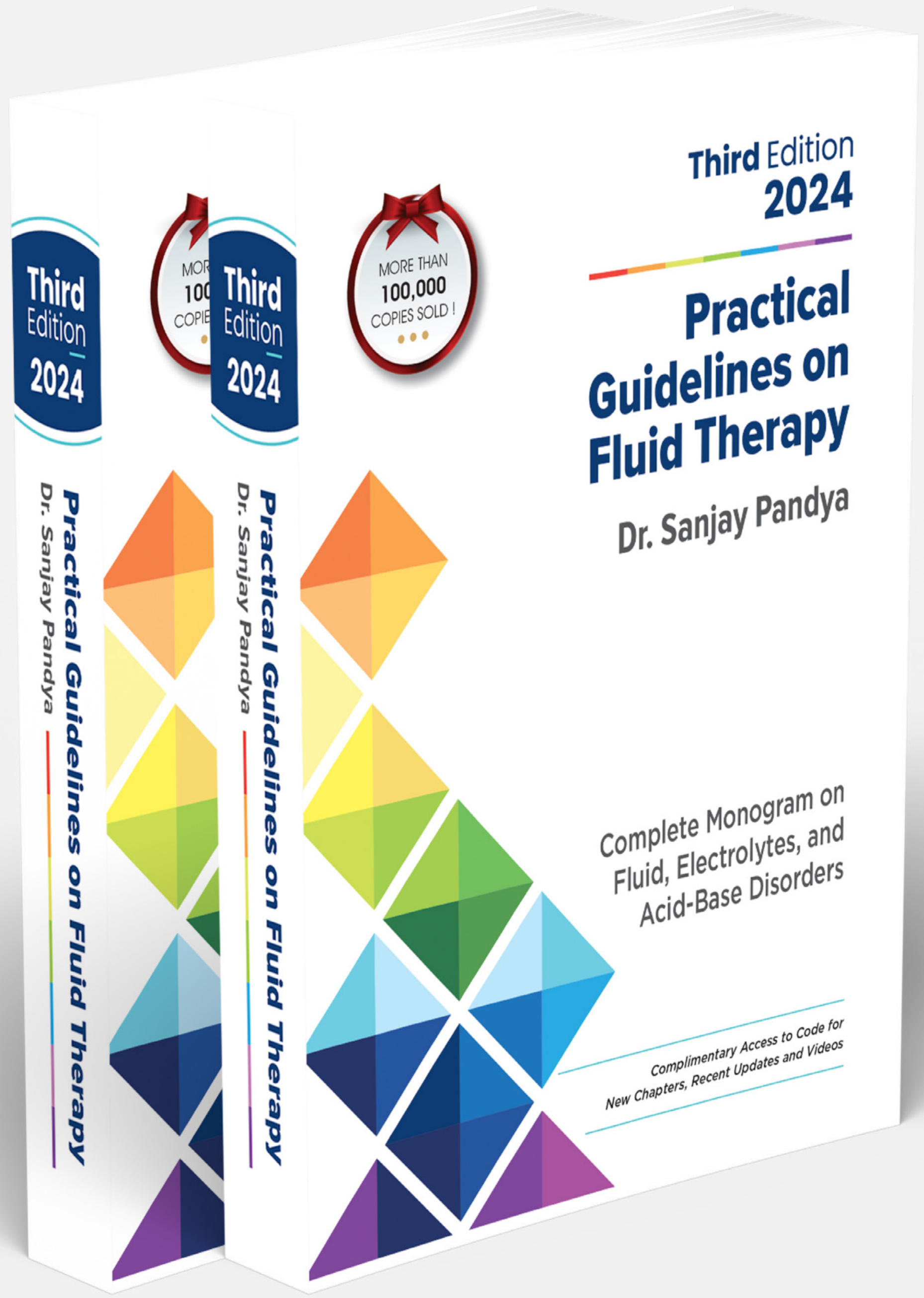
Chapter 45:

TURP Syndrome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45 TURP Syndrome

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Transurethral resection of prostrate (TURP) is the second most common surgical procedure (after cataract extraction) done in men over the age of 65 years. Transurethral resection of prostrate syndrome is rare but potentially dreaded complication of urological endoscopic surgery [1].

DEFINITION

TURP syndrome is a distinct clinical entity characterized by a constellation of sign-symptoms secondary to neurological, cardiovascular and electrolyte imbalance resulting from the absorption of the irrigation fluid through prostatic venous sinusoids or breaches in the prostatic capsule during TURP.

INCIDENCE

The prevalence of TURP syndrome, previously reported to be as high as 2% to 12% in earlier literature, [2, 3], has significantly decreased to 1% or less with the adoption of safer techniques, as demonstrated in recent literature [4, 5].

RISK FACTORS

Following patient and technique-related factors carry a high likelihood of developing TURP syndrome [1, 6–8]:

- Patient-related factors contributing to the development of TURP syndrome include age over 80 years, prostate weight exceeding 75 gm, and resected prostate weight over 45 gm.
- Technique-related factors contributing to fluid absorption during TURP and the development of TURP syndrome include resection time over 90 minutes using Monopolar electrosurgery technique, the use of hypotonic irrigation fluid, irrigation volume greater than 30 liters, high irrigation pressure (height >70 cm), inadequate effluent through the

resectoscope, intermittent drainage of fluid, the use of a monopolar instead of a bipolar diathermy system, and an inexperienced surgeon.

ROLE OF IRRIGATION FLUID

The type of irrigation fluid used during TURP surgery can influence the risk of TURP syndrome, with hypotonic irrigation fluids specifically posing an increased risk for its development. Commonly used solutions in TURP include both non-electrolyte solutions like distilled water, 1.5% glycine, 5% dextrose, sorbitol, and mannitol solutions, as well as electrolyte solutions such as normal saline and Ringer's lactate.

A. Distilled sterile water

Due to its affordability, easy availability, and superior visualization compared to 1.5% glycine and normal saline, distilled water is frequently utilized as a substitute for glycine in TURP in resource-limited settings of low-income countries [9, 10]. Due to its extreme hypotonicity compared to glycine and other irrigation fluids, distilled water carries a higher risk of TURP syndrome, including risks of haemolysis, dilutional hyponatremia, shock, and renal failure [11]. Due to high risk of severe adverse effects, currently most of centers do not use distilled water for TURP.

B. Glycine

Irrigation fluid, specifically glycine 1.5% with an osmolality of 200 mOsm/L, is widely utilized for the traditional therapeutic endoscopic urologic procedure TURP. It is preferred due to its favorable characteristics, such as low electrical conductivity and a refractive index similar to water, ensuring clear vision during the procedure. Despite its hypotonic osmolality, glycine is nonhemolytic as it effectively penetrates red blood cells, maintaining their structural integrity and preventing cell swelling or rupture. However, it is crucial to note that the osmolality of 1.5% glycine at 200 mOsm/L can cause serum electrolyte dilution and result in hyponatremia due to its large volume absorption. It is important to be aware that the rapid absorption of glycine can be toxic, leading to increased plasma ammonia levels and potential adverse effects such as cardiodepressant effects and renal toxicity [12]. Due to potential risk of metabolic and electrolyte disturbances, and the availability of safer options, trend to use glycine as preferred irrigation fluid for TURP is declining [13, 14].

C. Normal saline

An isotonic irrigation fluid, normal saline, is commonly used as the preferred and safer choice for TURP but can only be utilized when employing the bipolar electrosurgery technique [15, 16]. The risk of hyponatremia and TURP syndrome is very low when saline is used as an irrigation fluid for TURP, due to its slightly higher sodium concentration and osmolality compared to plasma (154 mEq/L vs. 140 mEq/L and 308 mOsm/L vs. 290 mOsm/L, respectively) [13, 17, 18]. However, it is important to note that the absorption of a large volume of normal saline can lead to adverse effects such as volume overload, heart failure, and hyperchloremic metabolic acidosis [15, 19, 20].

Caution: Do not use normal saline while using monopolar electrosurgery for TURP because saline conducts electricity and diffuses the current, making conventional monopolar cautery ineffective for cutting or coagulating.

Irrigation fluids like 5% dextrose, sorbitol and mannitol are used less frequently.

PATHOPHYSIOLOGY

During a TURP procedure, irrigation fluid can be absorbed through the prostatic venous sinuses or directly into the systemic circulation via disrupted venous channels, resulting in systemic effects due to rapid changes in osmolality and circulating volume [21]. The severity of TURP syndrome is closely related to the rate, volume, and composition of the systemically absorbed irrigation fluid. Various factors influence these factors, including electrolyte concentrations, osmolality, solute content, irrigation fluid delivery pressures, surgery duration, and surgical skill.

Major disturbances due to TURP syndrome are summarized below:

A. Circulatory overload

The average rate of irrigation fluid absorption through the venous network of the prostatic bed during TURP is reported to be 10–30 ml/min of operating time [22]. Typically, approximately 1 liter of fluid is absorbed within one hour. However, when a larger volume of fluid is absorbed, it can result in increased blood volume, leading to circulatory overload. This, in turn, can cause elevated systolic and diastolic blood pressure and potentially lead to heart failure, resulting in pulmonary edema.

B. Dilution and hyponatremia

The excessive absorption of hypotonic irrigating fluids, such as distilled water, 1.5% glycine, or sorbitol, during TURP can lead to the dilution of serum electrolytes, resulting in hyponatremia. This dilution, caused by the hypotonic fluid, increases the water content within the brain, which can potentially cause neurological symptoms.

C. Hemolysis due to hypotonic fluid

When a hypotonic irrigation fluid, such as sterile water, is absorbed in a large volume, its hypotonicity can result in the movement of water into red blood cells, leading to their swelling and potential rupture, which can cause hemolysis. The release of hemoglobin from ruptured cells can contribute to complications such as renal dysfunction and coagulopathy.

SIGNS AND SYMPTOMS

TURP syndrome can manifest with variable clinical presentations, ranging from mild cases that may go unnoticed to severe and life-threatening situations. The severity of symptoms depends on the extent of the abrupt reduction in serum osmolarity, which leads to hyponatremia, as well as the severity of volume overload and intravascular hemolysis.

The earliest common clinical presentation of TURP syndrome includes headaches, anxiety, nausea, bradycardia, irritability, confusion, and visual disturbances, such as flashing lights [23, 24]. Development of intraoperative hypertension is indicative of hypervolemia.

In severe cases of TURP syndrome, the clinical presentation can be life-threatening and may include profound hyponatremia, leading to neurological symptoms such as altered mental status, stupor, seizure, and even coma. Patients may experience severe cardiovascular instability, causing dyspnea, chest pain, hypoxia, and pulmonary edema. If not treated promptly, the patient may develop cyanosis, hypotension, and even cardiac arrest. Additionally, the presence of hemolysis may manifest as hematuria, jaundice, and acute kidney injury, while hypothermia can occur due to the rapid absorption of large volumes of irrigation fluid.

Diagnosis of TURP syndrome is difficult and often delayed when TURP is done under general anesthesia. Unexplained hypertension and refractory bradycardia are the very important warning signs of TURP syndrome. Therefore, all patients undergoing TURP should be closely monitored with electrocardiogram (ECG) and frequent blood pressure monitoring.

Patients with TURP syndrome can experience symptoms related to the toxicity of solute contents in irrigation fluid, such as glycine-induced visual abnormalities and sorbitol-induced gastrointestinal disturbances.

PREVENTION

Measures used to minimize the risk of complication TURP Syndrome include [1, 5, 25–27]:

- **Patient selection:** Identify individuals at higher risk of TURP syndrome and correct possible modifiable factors. Patients with preexisting hyponatremia are at greater risk of developing TURP syndrome, so patients on a salt-restricted diet or diuretic therapy need correction before surgery.
- **Selecting an appropriate irrigation fluid:** Isotonic solutions, such as normal saline, are preferred to minimize the risk of hyponatremia [28]. To prevent TURP Syndrome, it is advisable to restrict volume or avoid using hypotonic fluids like glycine and sterile or distilled water.
- **Fluid limitation:** Careful monitoring and limiting the volume of irrigation fluid used during TURP procedure can help prevent excessive fluid absorption. Sparingly use intravenous fluids, if needed and avoid the use of hypotonic IV fluids to minimize the risk of TURP syndrome.
- **Bipolar TURP:** The new system, bipolar TURP, is preferred over the monopolar TURP system because it uses normal saline for irrigation, maintaining the balance of electrolytes and preventing TURP syndrome [29, 30]. The bipolar TURP procedure allows the use of isotonic electrolyte solutions like normal saline for irrigation, unlike the monopolar TURP technique, where non-electrolyte hypotonic irrigation fluids are used, carrying a high risk of TURP syndrome [5].
- **Operative modifications:** Various intraoperative measures that can help prevent TURP syndrome include keeping the patient horizontal and avoiding the Trendelenburg position, limiting resection time to one hour, considering staged procedures for resecting large prostates to avoid prolonged operative times, and preserving the prostatic capsule by avoiding aggressive resection near it.
- **Fluid bag height:** The rate of fluid absorption during TURP is influenced by the hydrostatic pressure of the irrigation fluid at the prostatic bed. To prevent excessive absorption, it is important to deliver the irrigation fluid at the lowest required pressure and avoid setting the fluid bag height greater than 60 cm above the patient.
- **Avoid increased bladder pressure:** Ensuring smooth bladder drainage is the most crucial factor in minimizing fluid absorption during TURP and preventing TURP syndrome, which can be achieved by implementing the following methods: suprapubic continuous drainage using Reiter's cannula or trocar cystostomy, utilizing a continuous flow irrigation system, and using a large diameter catheter to maintain low bladder pressure.
- **Experienced surgeons:** Having TURP procedures performed by experienced surgeons can reduce complications,

shorten surgical times, and improve outcomes.

- **Using regional anesthesia:** Performing a TURP under spinal or epidural anesthesia is preferred because the awake and alert state allows for early diagnosis of TURP syndrome, whereas general anesthesia may mask its symptoms [23, 24].
- **Monitoring during TURP:** Continuous monitoring of the patient's vital signs can help detect early signs of TURP syndrome. Measure the quantity of fluid absorbed and stop the procedure at predetermined absorption thresholds.
- **Early intervention:** Prompt recognition of TURP syndrome symptoms and immediate intervention including use of diuretics, can prevent the progression to severe or life-threatening complications.

MANAGEMENT

Early and prompt treatment of TURP syndrome will prevent its serious central nervous system and cardiac complications. The treatment is planned according to the severity of the symptoms, and in asymptomatic patients with mild hyponatremia, specific therapy is not necessary. The treatment of symptomatic patients is summarized below [21, 23].

A. Termination of surgery

When TURP syndrome is diagnosed, the surgical procedure is terminated as early as possible.

B. Diuretics and fluid restriction

Discontinue IV fluids and administer furosemide at 1 mg/kg to increase renal water excretion, leading to an increased urine output, which helps eliminate large volumes of absorbed irrigation fluid and reduces circulatory overload.

C. Hypertonic saline

To correct severe hyponatremia in symptomatic patients with severe neurological symptoms, such as severe headaches, confusion, altered sensorium, convulsions, and coma, administer 100 ml of 3% hypertonic saline rapidly (to be given over 20 minutes) along with IV furosemide. In cases of acute severe hyponatremia, the administration of 3% NaCl as a rapid intermittent bolus (RIB) is preferred over slow continuous infusion, as recommended for the treatment of acute hyponatremia in recent guidelines. [31–33]. To guide further administration of 3% saline, measure serum sodium and its rate of correction by frequent estimation, and closely monitor the neurological status. Continue 3% saline until neurological symptoms improve.

D. Hemodialysis

Hemodialysis is indicated in a few severe cases of TURP syndrome characterized by marked hyponatremia, volume overload, and acute kidney injury. In such cases, diuretics may be less effective, and hemodialysis effectively corrects hyponatremia, removes excess fluid, and eliminates toxic metabolites of irrigation fluids such as glycine, sorbitol, or mannitol.

E. Supportive measures

This involves administering oxygen to treat pulmonary edema and hypoxia, managing seizures with medications such as diazepam, barbiturates, or dilantin, using inotropes to treat hypotension, correcting hypocalcemia, and cautiously transfusing blood with packed red cells to manage anemia.

MONITORING

Monitoring of the management of TURP syndrome includes:

- Continuous monitoring of vital signs, such as blood pressure, heart rate, and oxygen levels, to assess the patient's overall condition.

- Assessing neurological status for any improvement or deterioration in symptoms.
- Meticulous volume assessment, maintaining strict intake-output charting and daily weight to assess the correction of volume overload, plan fluid intake, and adjust diuretic dosages.
- Closely monitoring laboratory tests, including serum electrolytes (especially sodium), osmolality, renal function tests, complete blood count (CBC), and coagulation profile.

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Chapter 46:

Burns

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Fluid management in burns is a crucial aspect of burn care as it significantly impacts patient outcomes, particularly in severe cases where larger volumes of IV fluids must be administered within the first hours, exceeding the needs of other trauma patients [1].

However, it is a complex and controversial topic, as no one-size-fits-all approach can be universally applied to every clinical scenario. Therefore, it is essential to have a comprehensive understanding of fluid therapy in order to make proper decisions regarding the selection, volume, and administration of fluids from the array of available fluid regimens.

IMPORTANCE OF FLUID MANAGEMENT

Effective, optimal, and timely fluid management is crucial for resuscitation in burn patients because:

- Severe hypovolemia and hypotension in severe burns can lead to life-threatening shock or shock-induced renal failure [2].
- Delayed or insufficient fluid resuscitation is associated with higher mortality [3].
- Severe hypotension and suboptimal fluid resuscitation cause rapid conversion of viable but ischemic

deep-dermal burn to non-viable full-thickness burn, leading to greater mortality [4].

- Acute loss of protein (especially in the first 24 hours) due to leaky capillaries in the burned tissue causes hypoproteinemia, which accentuates edema formation in the burn as well as non-burn areas. Proper fluid therapy is essential for its prevention.
- Over-aggressive fluid therapy is harmful as it can lead to fluid creep and other complications [3, 5].

CAUSES OF HYPOTENSION

Causes of hypovolemia and hypotension in burns are multifactorial, including extensive loss of plasma from damaged blood vessels, increased capillary permeability, fluid shifts into the interstitial space, and loss of albumin and other proteins [6]. Additionally, the release of inflammatory mediators can lead to vasodilation and reduced systemic vascular resistance [7]Decreased cardiac output, which occurs in the early postinjury phase, also contributes to hypotension [8]. The combination of these factors can result in inadequate circulating blood volume and impaired tissue perfusion in burn patients.

GOALS

Providing timely and effective fluid resuscitation in burns is vital because a delay of more than 2 hours post-burn injury is associated with higher complications and mortality [4]. The objectives of proper fluid therapy in burns are:

- To restore and maintain adequate intravascular volume, optimize tissue perfusion, and improve oxygenation.
- To replace lost fluids, prevent complications such as hypovolemic shock and organ dysfunction, and correct electrolyte imbalances.
- To preserve heat-injured but viable soft tissue.
- To avoid the detrimental effects of over-resuscitation and associated complications like fluid creep.

INDICATIONS OF IV FLUIDS ADMINISTRATION

Common indications of intravenous fluid administration in burns are [9, 10]:

- Adults with more than 15–20% nonsuperficial burns.
- Children with more than 10% burns.
- Electric burns with hemochromogens in the urine.
- Patients at the extremes of age or elderly patients with preexisting cardiac or pulmonary disease, where the compensatory response to even minor hypovolemia is reduced.

Estimation of burn area: The "Rule of Nines" in burns is the most popular and quick method to estimate the percentage of total body surface area (TBSA) affected by burns: Head and neck (9%), each upper limb (front and back) (9% each, total 18%), anterior trunk (18%), posterior trunk (18%), each lower limb (front and back) (18% each, total 36%), and perineum (1%). The "Rule of Nines" provides a rough estimation but may not be precise for irregularly distributed burns or specific areas like the hands, feet, or face.

PLANNING FLUID THERAPY ON DIFFERENT POST-BURN DAYS

During the different stages of burns, the body undergoes varying degrees of fluid loss, resulting in the need for different volumes of fluids. Understanding the distinct pathophysiology during each stage is crucial for designing appropriate treatment strategies on different post-burn days.

For a basic understanding, fluid therapy in burns is broadly categorized into three phases:

A. Initial 24 hours
B. During the first 24–48 hours
C. Fluid therapy after 48 hours

A. INITIAL FLUID RESUSCITATION

During this period, the inflammatory response triggered by a burn injury results in increased capillary permeability and damaged blood vessels, leading to significant fluid loss from the blood vessels into the surrounding tissues. The leakage of fluid rich in sodium and proteins from the intravascular compartment into the interstitial spaces of the burn area contributes to the formation of edema. Hence, it is crucial to promptly and cautiously initiate IV fluid resuscitation during the initial phase to replace lost fluid, maintain blood pressure, and minimize edema formation.

Fluid therapy in burns is tailored based on factors such as the extent and degree of burn injury, hemodynamic status, coexisting morbid conditions, body weight, age, preexisting medical conditions, burn location, and time since the burn injury. To ensure adequate and effective fluid resuscitation during the initial phase of burns, it is crucial to establish appropriate vascular access, select the suitable replacement fluid, accurately determine the required fluid volume through proper calculations, and decide on the optimal rate of fluid administration.

Vascular access

Establishing vascular access is crucial for the timely and effective administration of large amounts of IV fluids, but it can be challenging in burn patients due to technical issues such as edema [11]. Commonly employed options for IV fluid administration include the reliable insertion of large bore IV in peripheral veins, with the utilization of vessels underlying burned skin if necessary. In cases where peripheral intravenous access is unavailable, alternatives such as tunneled central venous catheterization, central line placement, or the use of intraosseous access in emergent situations can be considered.

Choice of replacement fluid

The mainstays for initial fluid resuscitation in burns include the use of crystalloids like Ringer's lactate, normal saline, and PlasmaLyte, and colloids like albumin and hydroxyethyl starch. The selection of these fluids is individualized based on factors such as the severity of the burn, hemodynamic status, and response to therapy.

1. Crystalloid resuscitation

For initial fluid resuscitation in burns, the primary options are crystalloids such as Ringer's lactate, normal saline, and PlasmaLyte.

a. Ringer's lactate: Crystalloid solution Ringer's lactate (RL) is the recommended first-line intravenous fluid for initial fluid resuscitation in burns [9, 10, 12]. The preference for RL over normal saline is based on several reasons, which are as follows:

- RL is a balanced crystalloid solution that closely resembles plasma electrolyte composition, enabling the administration of large volumes without causing electrolyte imbalances.
- With a high sodium concentration of 130 mEq/L, RL effectively replaces the significant amount of sodium and water lost from the intravascular

space into the interstitial spaces of the burn area, correcting hypotension.

- RL is free of glucose, so it does not carry the risk of hyperglycemia and associated problems even when rapidly infused in large volumes.
- RL's conversion of lactate into bicarbonate helps correct metabolic acidosis commonly seen in burn patients.
- Using RL instead of normal saline for initial fluid resuscitation in burns prevents the risk of hyperchloremic acidosis associated with large volumes of normal saline.

b. Normal saline: Normal saline is an isotonic crystalloid solution that is widely available, inexpensive, and compatible with most medications. However, due to its 50% higher chloride concentration than plasma (154 mEq/L vs. 100 mEq/L), administering normal saline in large volumes can result in dilutional hyperchloremic acidosis, which makes it less favorable for initial fluid resuscitation in burns [3, 13]. Furthermore, normal saline lacks electrolytes such as potassium or calcium.

c. PlasmaLyte: PlasmaLyte, a newer balanced crystalloid solution similar to RL, is gaining popularity for its use in critically ill patients, including those with burn injuries [14]. Its utilization as the primary crystalloid solution for large burns is increasing due to its favorable characteristics, including a composition closer to plasma than RL and lactate as a bicarbonate precursor that can be metabolized even in patients with shock [15, 16]. However, the limited use of this fluid in burns is attributed to its high cost and the lack of evidence demonstrating its superiority over other fluids in burn management [17].

2. Colloid resuscitation

Colloids like albumin and fresh frozen plasma are commonly used, while hydroxyethyl starch and gelatins are avoided. The role of colloids in the initial resuscitation of burns is controversial, as their use is typically considered an adjunct to crystalloids rather than a primary choice of fluid. The limited utilization of colloids is primarily attributed to their higher cost and the absence of survival benefits [3, 18].

Capillary leakage is maximum within the initial 8 hours after the burn and persists for subsequent 24–48 hours [19]. Consequently, the use of colloids for resuscitation is generally avoided during the initial 8–12 hours, as it has minimal effect on intravascular retention due to the significantly high protein leakage [12, 20]. Furthermore, the use of colloids within 12 hours of a burn injury may have detrimental effects, as it can potentially worsen alveolar exudative inflammation [21].

However, judicious administration of colloids after 12–18 hours provides advantages, such as a reduction in the overall fluid volume requirement, a significant decrease in fluid load, and a minimized risk of "fluid creep" and edema formation [5, 18, 22].

a. Human albumin: Human albumin, the most widely used colloid, is recommended as an adjunct to crystalloid resuscitation in patients with severe burns and shock, particularly after the initial 12 to 18 hours [21]. Its major benefit lies in reducing the total volume requirement of crystalloid in burn patients during the early period, thereby reducing the risk of fluid overload and fluid creep [1, 23–28]. The use of albumin is suggested in patients with severe burns who have serum albumin concentrations below 30 gm/L [21] and a projected fluid volume requirement exceeding 6 mL/kg/%TBSA in 24 hours [29]. Notably, albumin administration decreases the occurrence of compartment syndrome, improves outcomes, and reduces mortality rates in patients undergoing burn shock resuscitation [25, 30].

b. Fresh frozen plasma (FFP): Natural colloids like human albumin and fresh frozen plasma are widely prescribed [31] and advocated in major burns [1, 19]. The use of FFP in burn resuscitation remains controversial, but recent literature suggests a growing trend of using FFP as a potential adjunct to crystalloids and as an alternative to albumin in severe burns because [32–35]:

- FFP effectively reduces the large amounts of crystalloid fluids required during burn resuscitation [18, 32, 36].
- Its composition is more consistent with the lost body fluid [21].
- FFP improves clotting factors and hemostasis and has a longer shelf life compared to albumin [37].
- FFP exerts a protective effect on the endothelium in burns by preventing the disruption of the endothelial glycocalyx, thus reducing the microvascular leak commonly associated with large burns [33, 38, 39].
- In the first study comparing FFP and albumin recently conducted, patients treated with FFP had significantly lower mortality [40]. However, further studies with larger sample sizes are needed to confirm these findings.
- FFP is preferred over albumin in certain guidelines [21].
- The risk of transfusion-transmitted infections is low due to recent advancements in screening techniques and more rigorous testing [41].
- In many resource-limited countries like India, FFP is preferred due to the limited availability and comparatively high cost of albumin [42]. However, the cost comparison between the two varies across different countries.

c. Hydroxyethyl starch: When hydroxyethyl starch (HES) was added to RL in severe burn injury, studies did not find a volume-sparing effect [43], and due to the lack of benefits and the increased risk of mortality, acute kidney injury and coagulopathy associated with HES [44, 45], recommendations strongly advise against its use in burns [46].

d. Gelatin: Gelatins are not recommended in burns as they have not shown superiority over crystalloids, and the evidence does not support their safety [1].

3. Hypertonic resuscitation fluid

Physiological considerations: Due to the distribution of sodium in the extracellular fluid (ECF), the sodium concentration of an IV fluid determines its ability to expand the ECF, including the intravascular volume, which plays a crucial role in maintaining hemodynamic stability. Due to its higher sodium concentration of 513 mEq/L, a smaller volume of 3% hypertonic saline is required for initial resuscitation compared to Ringer’s lactate, which has a sodium concentration of 130 mEq/L. The osmolality of 3% hypertonic saline solution, which is significantly higher at 1027 mOsm/kg compared to the normal serum osmolality of around 285 mOsm/kg, creates an osmotic gradient.

Clinical considerations: Hypertonic fluid resuscitation is considered an attractive choice as it increases plasma osmolality, shifts water into the intravascular space, reduces intracellular water volume, limits the development of cellular edema, and also reduces the requirements of total resuscitation fluid volume and prevents fluid creep [9, 18]. However, its use should be approached cautiously due to the potential risks of hypernatremia, hyperchloremia, renal failure, and increased mortality rate [9, 47]. Based on current data, the use of hypertonic saline as a safe and viable adjunct to burn resuscitation is not supported [34].

Formulas used to calculate fluid volume

Numerous formulas have been proposed to calculate the appropriate resuscitative volume, but it is important to remember that these formulas serve as rough guides for predicting initial fluid resuscitation [48]. Subsequent infusion rates should be adjusted hourly based on individual responses rather than blindly following a set regimen.

The Parkland and modified Brooke formulas are the two most widely used and popular formulas for calculation in adults. It is important to note that the 24 hours for resuscitation is calculated from the time of the burn accident and not from the time of admission or initiation of treatment. It is also important to note that this formula provides an initial estimate and may require adjustments based on hourly urine output, the patient's clinical condition, and ongoing assessment of their fluid status.

1. Parkland formula: The Parkland formula, also known as the Baxter Formula, was developed in 1968 by Baxter and Shires, and it remains the most frequently used formula for calculating the volume required for burn resuscitation. The estimated requirement of Ringer's lactate for patients with burns in the first 24 hours can be calculated using the widely used Parkland formula as follows [49]:

The Volume Required (ml) =
4 × %TBSA of Burns ×
Body Weight (kg)

For example, if a patient weighs 70 kilograms and has a burn affecting 30% of their TBSA, the fluid requirement in the first 24 hours would be:

Fluid Volume =
4 mL × 30% × 70 kg
= 8,400 mL or 8.4 Liters

Out of the total fluid requirement for the first 24 hours, half is administered within the first 8 hours following the burn injury, while the remaining half is given over the next 16 hours. This initial 50% volume administration within the first 8 hours is necessary to compensate for the maximum capillary leakage and the loss of protein and sodium-rich fluids that occur during this time. As the rate of fluid loss decreases after the initial 8 hours, a smaller volume is needed to meet the ongoing needs.

The calculated fluid should be administered as a continuous infusion at a constant flow rate, as administering a large amount of intravenous fluid in bolus form can result in increased edema, while slower infusion rates can lead to hemodynamic instability [50].

2. Modified Brooke formula: The modified Brooke formula provides a lower total volume for fluid resuscitation, aiming to prevent "fluid creep" or excessive fluid administration. The formula is as follows:

The Volume Required (ml) =
2 × %TBSA of Burns ×
Body Weight (kg)

3. American Burn Association guideline: According to the American Burn Association (2008) recommendation, the initial rate of crystalloid fluid resuscitation in the first 24 hours post-burn is estimated to be 2–4 mL/kg/% TBSA [9]. This guideline is derived from the modified Brooke and Parkland formulas, which are widely used and accepted for burn resuscitation.

4. WHO formula for mass burn casualties: In 2021, the World Health Organization Technical Working Group on Burns (WHO TWGB) recommended an initial fluid rate of 100 mL/kg/24 h, either orally or intravenously, as a resuscitation formula for burns beyond 20% TBSA (total body surface area), which is suitable for resource-limited situations [51]. This formula offers the advantages of simplicity, usability, and safety for primary management, including transfers, while reducing the risk of early complications, particularly in situations such as mass burn casualties when immediate expertise is not readily available [52].

Altered fluid requirement in patients with burns: Patients who typically require a large resuscitation fluid volume include those with full-thickness burns, high voltage electric injury, inhalation injury, and those who need escharotomy, whereas obese burn patients generally have lower requirements for resuscitation fluid volumes.

Volume overload and fluid creep

Several reports have documented a high incidence of receiving more resuscitation fluid than predicted, leading to volume overload when utilizing the Parkland formula for calculating fluid requirements [48, 53–55].

Fluid creep in burns refers to the inadvertent accumulation of excessive fluid in the body due to overly aggressive fluid resuscitation, which can result in complications such as tissue edema, compartment syndromes, infections, pneumonia, acute respiratory distress syndrome (ARDS), respiratory failure, acute kidney injury (AKI), increased need for renal replacement therapy (RRT), multiorgan failure, and even death [5, 55–58].

Several factors contribute to the development of fluid creep, including the overestimation of burn size, errors in judgment due to a lack of experience, overly enthusiastic or inattentive resuscitation practices, failure to recognize the need for colloids to conserve crystalloid administration in large volumes, inadequate monitoring of urine output, and inability to adjust fluid administration based on individual patient response [59].

To prevent fluid creep, several measures can be employed, including:

- Following an early fluid restriction regimen [29, 57, 60].
- Administering colloids such as albumin or fresh frozen plasma alongside crystalloids in cases with high fluid requirements, aiming to reduce overall fluid needs and minimize the risk of fluid creep [5, 18, 22, 26, 61].
- Avoid routine use of fluid boluses to correct hypotension.
- Implementing permissive hypoperfusion, a safe and well-tolerated strategy in studies involving adults and children [60, 62].
- Close clinical monitoring, including hourly urine volume assessment and making timely fluid volume adjustments as necessary.

Blood transfusion

Patients with severe thermal burns may uncommonly require a blood transfusion to correct anemia, which can result from associated traumatic injury, blood loss during surgical procedures, decreased red blood cell production, increased red blood cell destruction, and iatrogenic blood testing [63, 64]. Implementing a restrictive transfusion strategy with a red blood cell transfusion threshold of 7 gm/dL is well tolerated, markedly reduces transfusion volume, and helps prevent numerous complications associated with aggressive transfusion [64–66]. Patients should receive blood transfusions one unit at a time unless they are hemodynamically unstable or actively bleeding, and before administering a second unit, reassessment of the patient is necessary [63].

B. SUBSEQUENT FLUID THERAPY

(During the first 24–48 Hours)

During the first 24–48 hours following burns, it is common for the patient's body weight to increase by 5–15% of their pre-injury level due to fluid retention [67]. The goal of fluid management during this stage is to ensure sufficient fluid administration to maintain hemodynamic stability while restricting the total volume of administered fluids to achieve euvolemia and avoid fluid overload and fluid creep.

During this stage, although increased capillary permeability persists, it is relatively less pronounced compared to the first 24 hours, potentially leading to a lower volume of fluid loss. Consequently, the total fluid requirements for the second 24 hours are reduced, usually by nearly half compared to the requirements of the first 24 hours, for resuscitation fluid [68]. The volume is adjusted based on the patient's response to resuscitation, closely monitoring parameters such as hourly urine volume and other indicators.

If adequate urine output is maintained for more than 2 hours during the first 24–48 hours, it suggests adequate fluid resuscitation and the patient is gradually switched to maintenance fluid [69]. While calculating the maintenance fluid volume in burns, consider normal maintenance fluid plus evaporative loss from the burned skin. Maintenance fluid can be administered either intravenously, using D5/0.45 NaCl + 20 mEq potassium chloride per liter, or through enteral feeds.

The use of colloids for resuscitation is beneficial at this stage due to the decreased capillary permeability. This decrease in permeability results in reduced loss of colloids from the intravascular compartment into the interstitial spaces, providing two advantages. Firstly, it allows greater intravascular retention, ensuring effective hemodynamic stability. Secondly, it reduces the risk of tissue edema by decreasing protein leakage. Colloids, such as albumin or fresh frozen plasma, can be administered as 20–60% of the calculated plasma volume, which helps reduce fluid requirements and minimize the risk of fluid overload.

C. FLUID THERAPY AFTER 48 HOURS

During this early post-resuscitation phase (48–72 hours), capillary permeability decreases, resulting in decreased fluid loss. The primary focus shifts from aggressive fluid resuscitation to maintaining a balanced crystalloid status. The volume of fluid required is typically reduced compared to the initial 48 hours, emphasizing the importance of adjusting fluid administration to prevent fluid overload while ensuring proper hydration and electrolyte balance.

After the initial 48 hours of resuscitation, the fluid requirement consists of the sum of normal maintenance requirements, replacement of abnormal evaporative water loss, and continuous loss of plasma.

Fluid therapy is initiated based on the calculated maintenance requirements (100 mL/kg for the first 10 kg, + 50 mL/kg for 10–20 kg, and + 20 mL/kg for >20 kg) and is closely monitored. To calculate the required volume of IV fluid, subtract any orally consumed or NGT-administered fluid from the estimated fluid requirements.The fluid regimen is adjusted according to the patient's response to resuscitation, ongoing fluid losses, and clinical parameters.

MONITORING

Monitoring the burn patient is an essential component of fluid resuscitation, as no resuscitation formula should be considered a "license" to put the patient on autopilot. Careful and precise monitoring, along with necessary adjustments in the regimen, is vital for achieving adequate fluid resuscitation tailored to each patient's needs. Modalities used to monitor patients with burns can be categorized into clinical monitoring, laboratory tests, noninvasive monitoring, and invasive monitoring.

Clinical monitoring

The American Burn Association recommends monitoring pulse, blood pressure, urine output, mental status, and oxygen saturation in patients with burns [9].

Heart rate: The pulse rate holds limited usefulness but surpasses blood pressure measurement in sensitivity when monitoring fluid therapy [3]. Typically, a pulse rate below 110 to 120 beats per minute in a young adult suggests adequate resuscitation. However, if the heart rate exceeds 140 beats per minute, persistent severe tachycardia may indicate hypovolemia, although it can also arise from untreated pain or agitation [12]. Weak pulses may be attributed to inadequate fluid resuscitation, peripheral edema, or pressure on blood vessels caused by elevated compartment pressures.

Blood pressure: Manual blood pressure measurements can be challenging, inaccurate, and potentially misleading in edematous or charred extremities due to the progressive attenuation of auditory blood pressure signals as edema develops beneath the burn wound.

Sensorium: Anxiety and restlessness can be early signs of hypovolemia and hypoxia, indicating the need for attention and correction.

Urine volume: Accurate measurement and monitoring of urine output are crucial, requiring a urinary catheter in all patients with burns ≥20% TBSA [12]. Hourly measurement of urine output serves as the primary indicator for assessing adequate fluid resuscitation, evaluating tissue perfusion, and guiding timely adjustments in volume administration [70, 71].

Measure the hourly volume of urine, calculate the urine output as mL/kg, and adjust the rate of fluid administration in response to the patient's urine output as follows [72]:

- If the urine output is <0.5 mL/kg/h, increase the rate of infusion based on the hourly urine volume. Additionally, considering a fluid challenge with 250 ml of Ringer's lactate in addition to the ongoing fluid may be considered.
- If the urine output is between 0.5 to 1 mL/kg/h, it suggests adequate fluid replacement. Therefore, the fluid infusion should be continued at the same ongoing rate, and reassessment should be done hourly.
- If the urine output is between 1–2 mL/kg/h, the fluid infusion rate should be reduced by 10%, and reassessment should be done hourly.
- If the urine output is >2 mL/kg/h, the fluid infusion rate should be reduced by 20%, and reassessment should be done hourly.

It's important to note that increased urine output can occur in patients undergoing diuretic therapy or with conditions like glycosuria, hypertonic saline infusion, or dextran infusion attributed to the clearance of an osmotic load. However, this elevated urine output does not accurately indicate the patient's volume status and may potentially worsen severely depleted intravascular volume.

Laboratory tests

The laboratory tests performed for monitoring burns depend on the severity and extent of the burns and typically include complete blood count, electrolyte levels, blood urea nitrogen, creatinine, serum lactate and glucose levels, creatine phosphokinase, and mixed venous blood gas analysis.

Serum lactate level is a commonly used and valuable monitoring tool for hemodynamic resuscitation in patients with burns, as it helps assess tissue perfusion and metabolic status [73]. Estimating serum lactate levels early, upon hospital admission and periodically thereafter, is helpful in assessing the adequacy of tissue perfusion. An increase in serum lactate levels suggests inadequate end-organ perfusion, while a reduction in serum lactate levels after fluid infusion indicates adequate fluid resuscitation in burns [74].

Mixed venous oxygen saturation (SvO_2) plays a crucial role in evaluating the patient's respiratory function, and a decrease in SvO_2 suggests inadequate end-organ perfusion.

Noninvasive monitoring

Noninvasive monitoring methods, such as noninvasive blood pressure (NIBP), pulse oximetry, continuous electrocardiogram (ECG) monitoring, ultrasonography, Transthoracic echocardiography, pulse-contour analysis, and transpulmonary thermodilution can be utilized effectively in burns for comprehensive and noninvasive assessment, if available [75–77].

Invasive monitoring

Invasive monitoring is beneficial for selected high-risk patients with large burns and complex comorbidities, and various techniques used for monitoring include central venous pressure, transesophageal echocardiography, transpulmonary thermodilution, arterial blood pressure, and pulmonary artery catheterization to optimize their management. However, evidence supporting patient outcomes benefits after major burn trauma due to invasive monitoring to guide fluid resuscitation is lacking [78].

ENDPOINTS OF BURN SHOCK RESUSCITATION

The clinical interpretation of hemodynamic status can be challenging, and there are no single parameters that definitively determine the endpoints of resuscitation in burns. Therefore, simultaneous consideration of various parameters is essential, which may suggest hemodynamic improvement and guide in optimizing fluid administration.

The primary indicators of the adequacy of resuscitation include improvement in mental status (normalization of sensorium), urine output of 0.5 to 1 mL/kg/h without osmotic diuresis, normalization of heart rate and blood pressure (mean arterial blood pressure >70 mm Hg), and a reduction in lactate concentration and base deficit values [79, 80]. Base excess, lactate levels, and their correction rates reliably predict mortality [79].

Patients who are hemodynamically unstable, with coexisting comorbidities such as renal, hepatic, or cardiovascular disease, or elderly persons may need advanced hemodynamic monitoring for better monitoring if available.

COMPLICATIONS OF FLUID RESUSCITATION

Volume overload and fluid creep are common problems in burns, as discussed.

In addition, large-volume resuscitation can lead to uncommon yet severe complications, which are described below:

- Abdominal compartment syndrome (ACS) is characterized by sustained intra-abdominal pressure (>20 mmHg) and new onset multiorgan dysfunction, including oliguria and decreased pulmonary compliance.
- Extremity compartment syndromes occur when there is an increase in pressure within a closed muscle compartment due to blood accumulation or soft tissue edema, resulting in impaired capillary flow to the enclosed muscle. These syndromes are characterized by clinical signs such as swelling, tightness, muscle pain, pallor, coolness of the distal extremity, and, in severe cases, late loss of pulses.
- Pulmonary complications in burns can manifest as pleural effusions, pulmonary edema, respiratory failure, and prolonged intubation, contributing to significant respiratory challenges.
- Orbital compartment syndrome, a rare yet devastating complication of over-resuscitation, occurs due to a rapid increase in intraocular pressure. It is a surgical emergency characterized by orbital pain, double vision, acute-onset vision loss, and features such as a fixed dilated pupil and ophthalmoplegia.

NUTRITION ROUTE AND TIMING

Paying attention to nutrition is crucial in burns because it is a hypermetabolic state characterized by increased catabolism leading to increased caloric and protein requirements, significant loss of protein and micronutrients caused by the compromised skin barrier, and the need for increased energy expenditure to compensate for heat loss through the exposed surface [81]. Timely and adequate nutritional support in burns provides essential nutrients for tissue healing, supports immune function, reduces the risk of infection, minimizes protein catabolism and maintains lean body mass, and promotes wound healing and overall recovery [82]. So, early nutrition should be initiated proactively rather than waiting to address it later.

Route: Oral feed, enteral nutrition (EN), and parenteral nutrition (PN) are all viable options for providing nutritional supplementation in burns.

Enteral nutrition is recommended as first-line nutrition support in hemodynamically stable burns patients if oral feeding is not possible or if patients cannot meet the increased nutritional requirements through oral feeding alone. EN is preferred, and PN is not recommended routinely in burns because of adverse effects like overfeeding, impaired immunity, liver failure, and higher mortality [82].

The preferred method for enteral nutrition is nasogastric (NG) tubes, but feeding by nasoduodenal and nasojejunal tubes is indicated in a few patients with delayed gastric emptying.

PN is administered in burn patients only when EN is not feasible, not tolerated (e.g., abdominal distention, high residuals, diarrhea), or is inadequate to meet desired total nutrient requirements [83].

Timing of nutrition support: In burn patients, early EN (within 24 hours) is as safe as late EN (after 24 hours) [84], and it is recommended to initiate early EN, preferably within the first 24 hours after a burn injury [83, 85].

The advantages of early enteral nutrition in burns are [85, 86]:

- Protection of the gastrointestinal tract, preventing increased bacterial translocation and reducing the risk of sepsis.
- Enhanced nutrient adequacy, preventing the development of malnutrition and nutrient depletion.
- Reduced rates of complications and infections, shorter hospital stays, lower costs, and decreased morbidity and mortality.

For comprehensive information on nutritional considerations in burns, including energy, protein, carbohydrate, and lipid requirements, as well as the role of glutamine and micronutrients, please refer to the Chapter 56 on "Parenteral Nutrition in Specific Disease".

OLIGURIA IN BURNS

Oliguria during the resuscitation period (first 48 hours post burns) is commonly due to inadequate resuscitation and is almost never an indicator of acute kidney injury. It should be treated with increased fluid administration, not by fluid restriction or administration of diuretics.

Patients with high voltage electric injuries, deep burns involving muscle, and associated crush injuries are prone to developing rhabdomyolysis and myoglobinuric acute kidney injury, which can lead to oliguria. Weakness, muscular pain, oliguria with dark red to brown urine, and significantly elevated creatine phosphokinase (CPK) levels suggest myoglobinuric acute kidney injury, which may need diuretics.

Urinary output is no longer a reliable indicator to monitor fluid resuscitation once a diuretic has been administered [12]. Diuretics are also required in patients with extensive burns who remain oliguric despite receiving fluid volume far over estimated needs.

FLUID IN HIGH VOLTAGE ELECTRIC INJURIES

Management of high voltage electric injury is more complex and challenging than standard burn resuscitation due to the potential presence of significant and extensive deep muscle injury that may be hidden beneath normal-looking skin, making it difficult to estimate the severity and extent of burns accurately [87]. Additionally, severe electric injuries can cause damage to deep tissues and muscles, leading to acute kidney injury through rhabdomyolysis-induced precipitation of urinary hemochromogens in the renal tubules.

In such cases, administration of additional fluid is necessary to achieve a high urine flow (0–1.5 ml per kg per hour or 75–100 ml/hour in adults) in order to facilitate the rapid clearance of heme pigments, thus eliminating the need for diuretics and preventing acute kidney injury [12]. As various formulas tend to underestimate the fluid requirements for resuscitation significantly, optimal fluid administration is more accurately guided by monitoring urine output and other clinical, laboratory, and hemodynamic parameters to determine appropriate resuscitation endpoints [87].

If oliguria persists despite adequate hydration, additional measures for diuresis can be employed, such as the use of osmotic diuretics (such as mannitol), loop diuretics (like furosemide), or urine alkalization through sodium bicarbonate titration.

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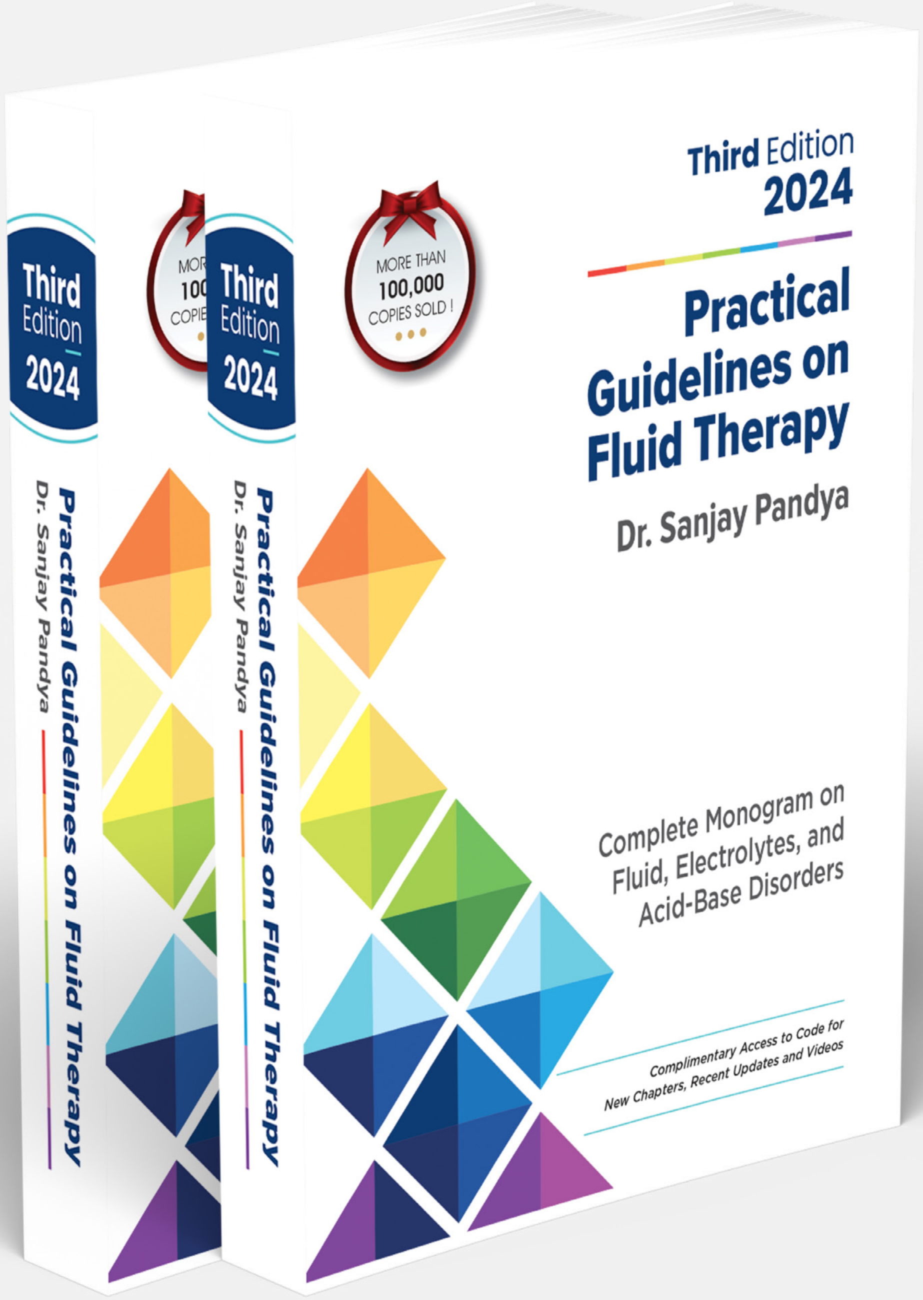
fluid

Chapter 47:

Urinary Diversion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47

Urinary Diversion

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Urinary diversion is a surgical procedure that creates a new route to reroute urine flow from the normal pathway to an alternate path for elimination from the body.

INDICATIONS

Urinary diversion becomes necessary when the bladder can no longer safely store urine due to various conditions, such as:

- Bladder carcinoma: Surgical removal of the bladder for carcinoma.
- Traumatic injuries: Extensive damage to the bladder, urethra, or pelvis.
- Medical conditions: Malfunctioning bladder due to neurologic bladder dysfunction.
- Congenital defect: Bladder exstrophy is a congenital condition in which the bladder is located outside the body.
- Miscellaneous causes: Severe radiation injury to the bladder, intractable urinary incontinence, or vesicovaginal fistulae.

METHODS OF URINARY DIVERSION

There are several types of urinary diversion procedures, and the choice of procedure depends on the specific medical condition, extent of urinary tract involvement, and personal preference [1].

Urinary diversions are classified into two types [2]:

1. Incontinent diversions, where urine is redirected into an intestinal segment and continuously drained into an external collection bag (e.g., ileal conduit).
2. Continent diversions, where urine is collected and stored within the body, requiring either self-catheterization (e.g., catheterizable ileal pouch) or voluntary voiding to empty the reservoir (e.g., orthotopic neobladder).

Four common methods of urinary diversion includes:

A. Ileal conduit urinary diversion

The most commonly performed and simplest type of incontinent urinary diversion with the fewest surgical complications involves attaching the ureters to a segment of the ileum, creating a stoma on the abdomen for continuous urine drainage into an external collecting bag. The drawbacks of ileal conduit urinary diversion include the need for an external collecting bag for continuous urine drainage, potential changes in body image, and the possibility of leakage or odors.

B. Ileal pouch urinary reservoir

In this continent cutaneous diversion method, a pouch is created from portions of the ileum to store urine within the abdomen. The ureters are redirected to drain into this pouch, and intermittent self-catheterization is required several times a day to empty the urine from the pouch. The advantages of the ileal pouch reservoir surgery include not requiring an external bag for urine collection and eliminating the issue of odor associated with external urine drainage.

C. Orthotopic neobladder

This is a form of continent urinary diversion in which a surgically created reservoir is made from a segment of the intestine and placed in the same anatomical position as the original bladder, connected to the urethra. The neobladder closely resembles the storage function of a urinary bladder, allowing patients to void normally by increasing intra-abdominal pressure and significantly improving their quality of life and self-image after radical cystectomy. If voiding is not adequate despite the aforementioned efforts, patients may need to perform self CIC (clean intermittent catheterization).

D. Ureterosigmoidostomy

This urinary diversion procedure involves connecting the ureters to the sigmoid colon, allowing urine to be diverted into the colon and eliminated with bowel movements.

Ureterosigmoidostomy, which was once a common urinary diversion procedure, is now rarely used and considered a last resort option due to potential risks, such as electrolyte imbalances, urinary tract infections, worsening of kidney function, and the risk of colon malignancy. Safer and more advanced methods of urinary diversion have largely replaced it. However, due to advantages such as providing urinary continence without the need for a stoma and external appliances, simplicity, and the relatively quick performance of the procedure, ureterosigmoidostomy is still performed in some complex pediatric cases in resource-limited settings [3].

PATHOPHYSIOLOGY OF METABOLIC AND ELECTROLYTE DISTURBANCES

The factors that determine metabolic derangements and electrolyte imbalances in urinary diversion include the type of bowel segment used for the anastomosis, the length and surface area of the bowel segment exposed to urine, and the duration of contact time between urine and the bowel [4].

Urinary diversions involve using a part of the bowel that is not physiologically designed to handle and withstand urine's fluid composition [5]. Metabolic and electrolyte imbalances are more common in traditional ureterosigmoidostomy compared to other newer methods of urinary diversion. In ureterosigmoidostomy, urine containing chloride, sodium, and ammonium is diverted to the sigmoid colon, which acts as a reservoir. Due to the sigmoid colon serving as a large-sized reservoir and the prolonged transit time of urine in the colonic segment, which leads to a longer contact period in the colon, there is a significant exchange of urinary electrolytes with plasma through the colonic mucosa, resulting in fluid and electrolyte disturbances.

Common abnormalities encountered in ureterosigmoidostomy include metabolic acidosis, hypokalemia, hyperammonemia, diarrhea, urolithiasis, and metabolic bone diseases.

A. Metabolic acidosis

Metabolic acidosis commonly occurs in urinary diversions when urine comes into contact with the bowel wall, leading to the reabsorption of urinary ammonia, hydrogen, and chloride in exchange for the excretion of sodium and bicarbonate ions, which contributes to its development [4].

The absorption of chloride-rich urine by the luminal anion exchange pump of the colonic mucosa leads to the secretion of HCO_3 in exchange, causing bicarbonate loss in the bowel and resulting in hyperchloremia and metabolic acidosis.

An additional mechanism contributing to the development of hyperchloremic acidosis in urinary diversion is the absorption of ammonium [4]. When urine comes into contact with the colonic mucosa, fecal bacteria convert urinary ammonia into a large amount of ammonium ions. This leads to excessive intestinal absorption of urinary ionized ammonium, along with chloride as ammonium chloride, causing a loss of bicarbonate and a gain of chloride, resulting in hyperchloremic metabolic acidosis [6]. Loss of bicarbonate due to diarrhea (due to colon irritation by urine) also contributes to hyperchloremic metabolic acidosis.

B. Hypokalemia

Hypokalemia is more common in sigmoid diversions compared to ileal diversions, possibly because the colon has a lower capacity for potassium absorption than the ileum. In ureterosigmoidostomy, hypokalemia develops due to both loss of potassium in the colonic mucosa (secretion) and renal wasting [7]. Renal potassium wasting plays a relatively major role in potassium depletion, and it occurs due to acidosis, volume depletion, and activation of the renin-angiotensin-aldosterone system [8]. Diarrhea due to colon irritation by urine leads to direct loss of potassium and contributes to hypokalemia.

C. Metabolic bone diseases

In patients with urinary diversion, the long-term risk of metabolic bone diseases is a concern, and the factors contributing to these conditions include [4, 5, 7, 9]:

- Demineralization of bone due to chronic metabolic acidosis.
- Metabolic acidosis impairs the renal activation of vitamin D, which is essential for proper bone mineralization.
- Hypomagnesemia in ureterosigmoidostomy, resulting from urinary loss of magnesium, can lead to hypoparathyroidism by reducing parathyroid hormone (PTH) release and causing PTH insensitivity, adversely affecting bone formation.
- Impaired intestinal absorption of both calcium and vitamin D occurs when

intestinal segments are used during diversion, leading to fat-soluble vitamin D deficiency, further aggravating bone demineralization.

- The associated presence of CKD contributes to metabolic bone diseases.

Metabolic bone diseases are late complications that can lead to osteomalacia and osteoporosis, increasing the risk of fractures [2].

D. Urolithiasis

The risk of renal stone formation is high (3% and 43%) in patients with ureterosigmoidostomy [10], and the mechanisms of its development are as follows [4, 5, 7, 11, 12]:

- Chronic metabolic acidosis leads to the release of bone calcium through the process of demineralization, resulting in hypercalciuria.
- Metabolic acidosis reduces urine citrate levels, and since citrate inhibits stone formation, a low concentration of citrate in the urine predisposes to the development of calcium-containing kidney stones.
- The increased intestinal absorption of bivalent anions, particularly sulfates, leads to elevated serum sulfate concentrations. The excretion of elevated urinary sulfate is coupled with the associated loss of urinary divalent cations, which can cause hypercalciuria and hypermagnesuria and raise the risk of stone formation.
- Dehydration due to diarrhea can lead to concentrated urine, which favors stone formation in the presence of the above predisposing factors.
- Anatomical changes that increase bacterial colonization, urinary stasis, mucus reflux into the upper tract, and exposure to surgical material such as sutures and staples may act as a nidus.

E. Hyperammonemia

In patients with ureterosigmoidostomy, urinary tract infections with urea-splitting organisms and urinary tract obstruction increase ammonia's production and subsequent colonic absorption significantly [13]. In patients with chronic liver disease or acute hepatic dysfunction, the liver cannot metabolize the increased ammonia load efficiently, leading to hyperammonemia and encephalopathy [4].

URINARY DIVERSION METHOD SELECTION

Selecting the appropriate urinary diversion method is crucial to prevent metabolic and electrolyte disturbances. In ureterosigmoidostomy, fluid and electrolyte disturbances are more common due to the larger capacity of the sigmoid colon and longer urinary contact time. To decrease these complications, the ileal conduit method for urinary diversion is effective because the ilial loop serves as a conduit and not as a reservoir. Urine is continuously drained into an external collecting bag, which reduces the contact time between urine and intestinal mucosa, thus minimizing the risk of metabolic and electrolyte disturbances. The incidence of stone formation is significantly lower with the ileal conduit diversion method, ranging from 9% to 11%, compared to 17% to 27% with the Kock pouch diversion [14].

The risk of metabolic and electrolyte disturbances is also reduced when methods like the ileal pouch urinary reservoir and orthotopic neobladder are used for urinary diversion, as they have smaller capacities, resulting in a smaller bowel surface area exposed to urine.

TREATMENT

Treating metabolic derangements and electrolyte imbalances in urinary diversion involves various approaches, depending on the specific imbalance present. Long-term planning with oral agents is desirable, as fluid and electrolyte abnormalities are usually chronic and persistent. In a few patients with severe dehydration, acidosis, and hypokalemia, vigorous hydration, alkalinization, and potassium repletion are needed [15].

A. Metabolic acidosis

Metabolic consequences and disturbances are frequently observed in patients following urinary diversion. Metabolic acidosis can lead to harmful effects in these patients, such as bone loss, increased protein catabolism, and decreased albumin synthesis, resulting in the loss of muscle mass and strength, making them frail and more susceptible to falls and fractures [2]. Initiating prophylactic treatment of metabolic acidosis early, at the stage of subclinical acidosis, and effectively restoring normal acid-base balance is crucial in preventing such metabolic complications [16].

The treatment for hyperchloremic metabolic acidosis requires administering alkalizing agents or blockers of chloride transport [8]. Alkalinizing therapy is commonly initiated with oral sodium bicarbonate (1–2 gm three times a day), but in some patients, it may cause significant gastrointestinal symptoms, such as excessive flatulence. Sodium citrate and citric acid (Shohl's solution) are used together as an effective alternative. Potassium citrate may also be used if excessive sodium administration is a problem (as in cardiac diseases) and potassium supplementation is desirable.

In patients with persistent hyperchloremic metabolic acidosis, where sodium loads are undesirable due to fluid retention/pulmonary edema and hypertension, chlorpromazine or nicotinic acid may be used to reduce the severity of acidosis. These agents impair chloride transport, limit the development of acidosis, and reduce the requirements for alkalizing agents rather than directly correcting the acidosis [8]. Chlorpromazine is usually given at a dose of 25 mg three times a day, whereas nicotinic acid is administered at a dose of 400 mg three to four times a day [17, 18].

Patients with ureterosigmoidostomy are advised to consume a low-sodium chloride diet to minimize their chloride intake and prevent acidosis [10].

B. Hypokalemia

Hypokalemia and total body potassium depletion are common in patients with ureterosigmoidostomies and are usually associated with hyperchloremic metabolic acidosis. Therefore, the treatment must involve simultaneous and cautious correction of both hypokalemia and metabolic acidosis.

In cases of severe potassium deficits, it is crucial to replace potassium before addressing the acidosis to avoid life-threatening hypokalemia. Conversely, correcting hypokalemia without treating metabolic acidosis can lead to hyperkalemia.

For prolonged oral correction, supplementing potassium citrate 15 mEq (approximately 1.6 gm b.i.d. to q.i.d.) helps in correcting both hypokalemia and acidosis in urinary diversion [19].

C. Metabolic bone diseases

Early and adequate correction of metabolic acidosis is crucial for preventing metabolic bone diseases and improving bone health; if the improvement is not achieved, oral calcium and vitamin D3 supplementation may be considered [9].

D. Hyperammonemia

Hyperammonemia can be managed through a low-protein diet and the administration of medications like oral neomycin and/or lactulose while simultaneously addressing disorders that can increase ammonia production, such as acute or chronic liver disease, urinary tract obstruction, and urinary tract infection [19].

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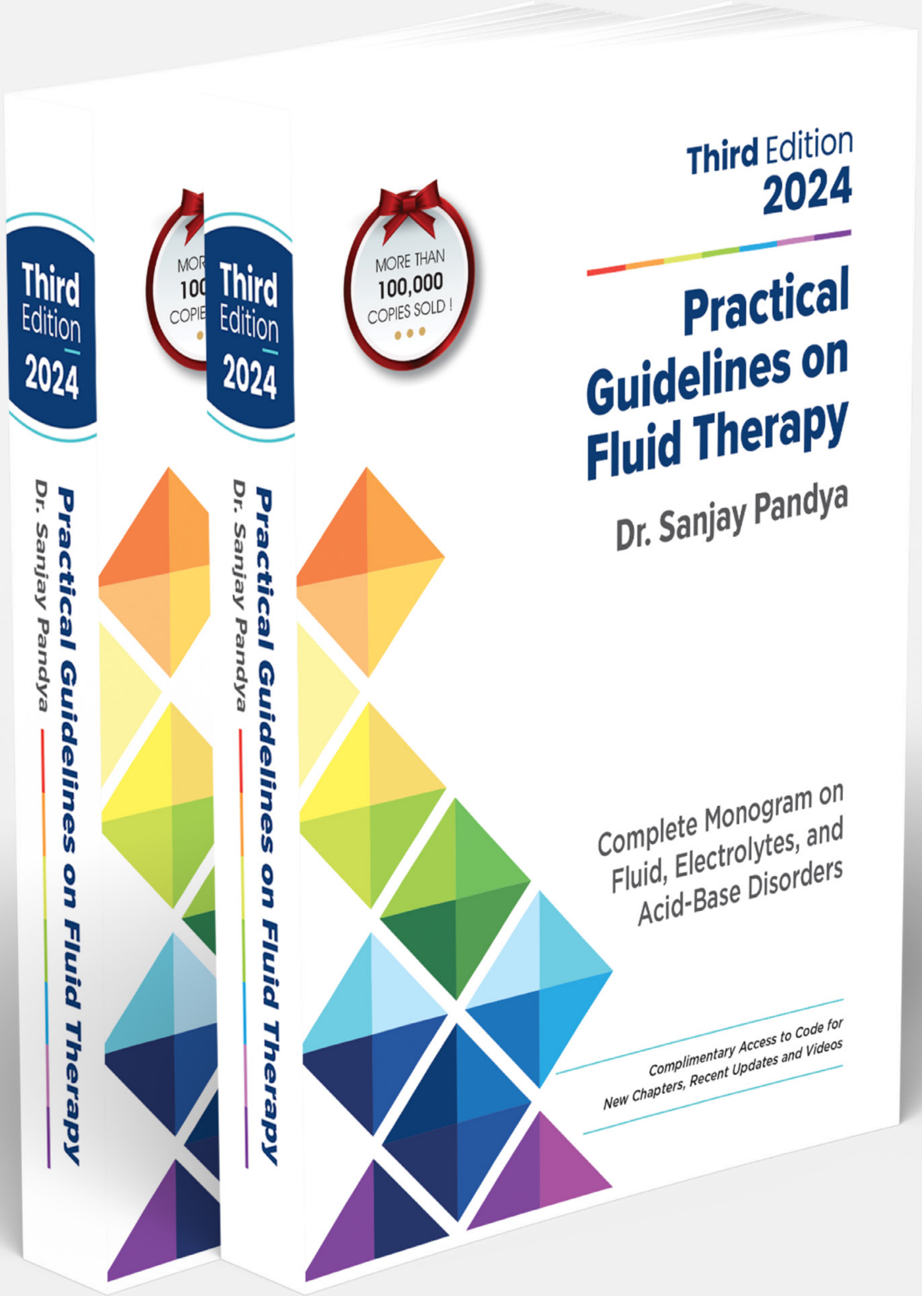
Chapter 48:

Resuscitation and Maintenance Fluid Therapy in Children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Resuscitation and Maintenance Fluid Therapy in Children

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Fluid therapy in children is an essential aspect of managing critically ill individuals, and appropriate fluid therapy can be lifesaving. The primary goal of resuscitation fluids is to establish hemodynamic stability, ensuring adequate intravascular volume and tissue perfusion. Maintenance fluids, on the other hand, are administered to achieve proper hydration and maintain electrolyte balance.

INDICATIONS OF IV FLUID THERAPY

Oral fluid replacement is always a safe and preferred mode. The indications of IV fluid therapy include correcting or maintaining fluid and electrolyte balance in conditions such as shock, severe dehydration, uncontrolled vomiting or diarrhea, inability to drink, paralytic ileus leading to abdominal distension, impaired sensorium, and other serious complications.

Goals: IV fluid replacement aims can be broadly categorized into three groups: Resuscitation, maintenance, and replacement [1]. Distinguishing these reasons is crucial because the choice of fluids, their composition, volume, and administration rates vary depending on the patient's clinical status and specific indications. It's essential to select the appropriate IV fluids tailored to each situation.

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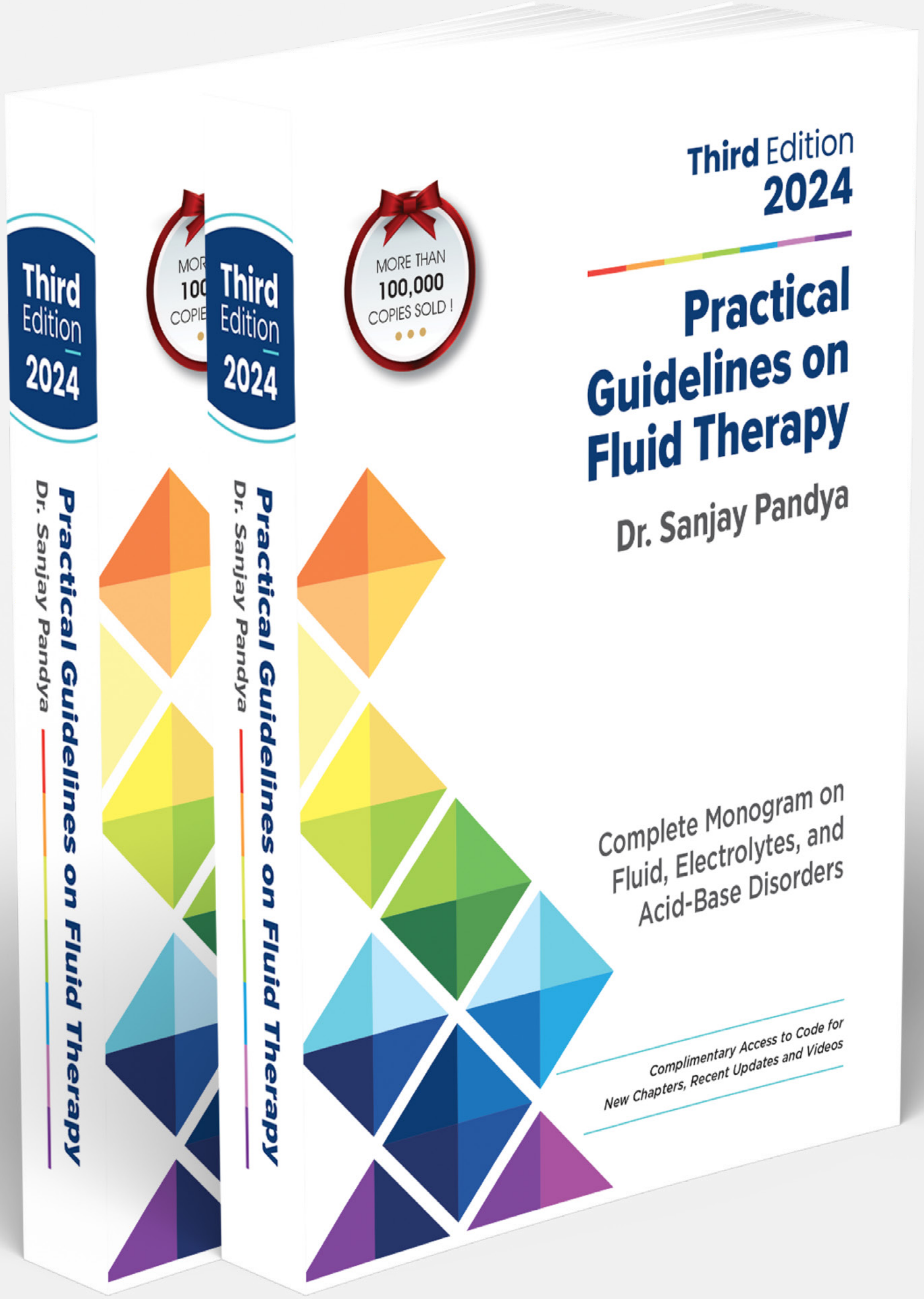
Chapter 49:

Replacement Fluid Therapy and its Monitoring in Children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Replacement Fluid Therapy and its Monitoring in Children

Assessment of the Severity of Dehydration **587**
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Replacement fluid therapy represents the third crucial pillar in comprehensive fluid management for children, complementing fluid resuscitation and maintenance strategies. IV fluids replacement aims to replenish preexisting deficits (fluids lost before treatment) and address ongoing losses, such as gastrointestinal issues due to vomiting and diarrhea, by administering the appropriate solutions to correct fluid, electrolyte, and acid-base disorders.

The five crucial steps to planning optimal and effective replacement fluid therapy in children are as follows:

1. Severity assessment: Assess the severity of dehydration, which can be categorized as mild, moderate, or severe.
2. Laboratory assessment: Utilize laboratory tests to evaluate dehydration in children.
3. Establish the type of dehydration: Determine the type of dehydration based on sodium concentration, specifically identifying if it is hyponatremic, isonatremic, or hypernatremic. Plan treatment based on this differentiation.
4. Identifying the underlying cause: Identify the etiology of fluid loss, such as diarrhea, vomiting, diabetic ketoacidosis, etc., and individualize treatment based on it.
5. Monitoring: Close clinical assessments, periodic laboratory tests, strict measurement of urine volume, and maintaining a daily weight chart help to assess the child's response to therapy, facilitating necessary adjustments based on their condition.

ASSESSMENT OF THE SEVERITY OF DEHYDRATION

The first step in replacement fluid management is to assess the severity of dehydration, which helps to decide both the urgency of intervention and the volume of fluid necessary for effective rehydration.

Determining the extent of dehydration involves three assessment steps: Asking specific questions, looking at visible signs, and physical examinations, as summarized in Table 49.1.

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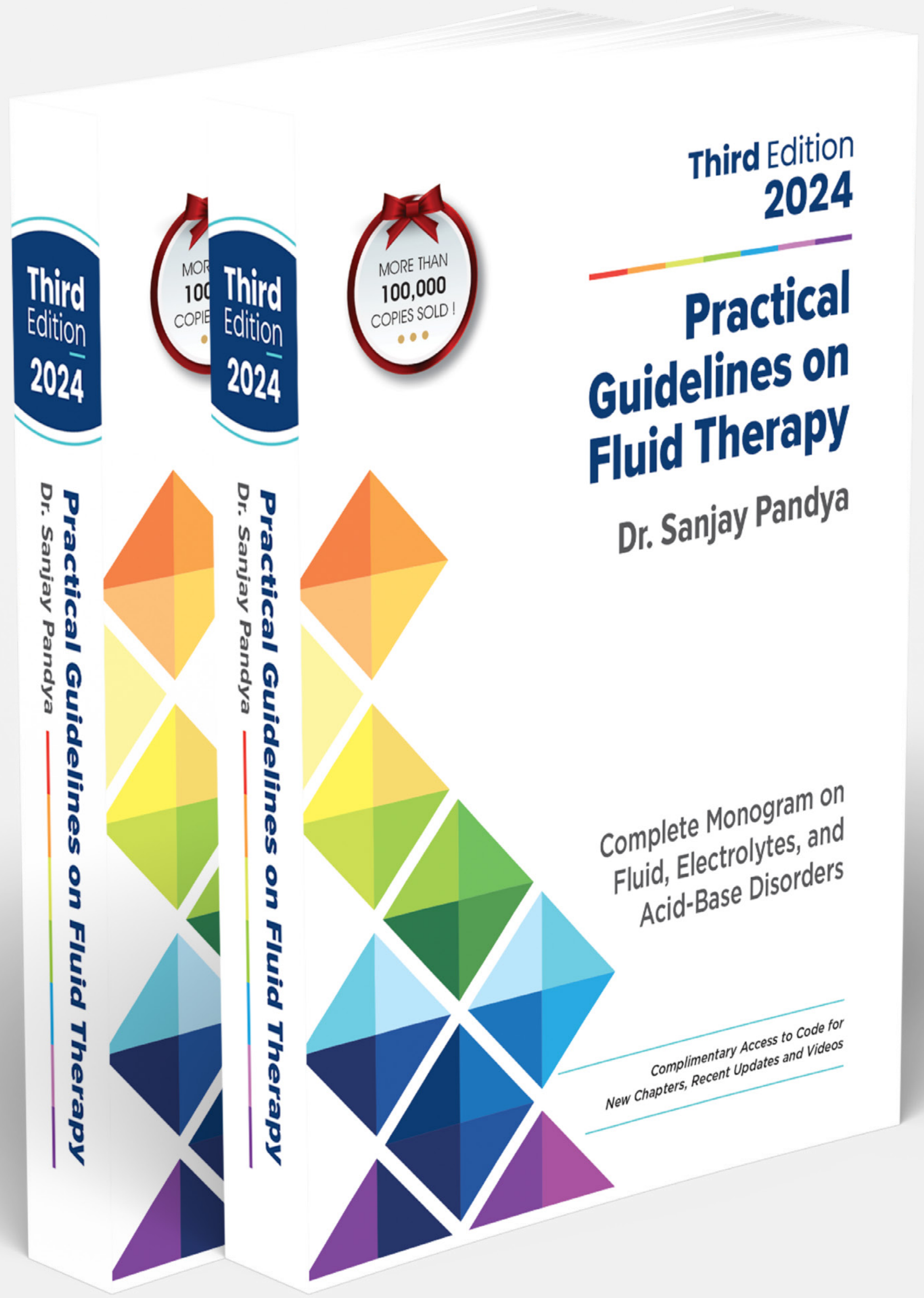
Chapter 50:

Oral Rehydration Therapy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Oral Rehydration Therapy

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Oral rehydration therapy (ORT) is a remarkable innovation that changed the outcome of millions of children suffering from diarrhea globally [1, 2]. ORT is a wonderful discovery that has saved more lives than any other treatment modality over the past century [3]. ORT is a cost-effective, noninvasive alternative to intravenous fluids, offering the benefits of being less expensive and having a lower complication rate.

ORT eliminates the need for IV fluid infusion, which requires a skilled professional to establish a venous line, especially in infants, and also avoids the risks of pulmonary edema or electrolyte imbalance associated with IV fluid therapy. The efficacy of ORT is often underestimated due to its low cost, leading to a lack of trust and subsequent underuse [4].

ORAL REHYDRATION SOLUTIONS VS. ORAL REHYDRATION THERAPY

The terms “oral rehydration therapy” and “oral rehydration solutions” are often used interchangeably. Oral rehydration therapy refers to the broader practice of using a variety of solutions, including oral rehydration solution (ORS), for rehydration, typically containing a mixture of salt, sugar, and water. On the other hand, ORS represents specific formulations, such as the WHO-recommended mixture of glucose and electrolytes, which are scientifically designed to treat dehydration effectively. Thus, ORS stands out as the most scientifically advanced and effective method for treating dehydration among all ORT options.

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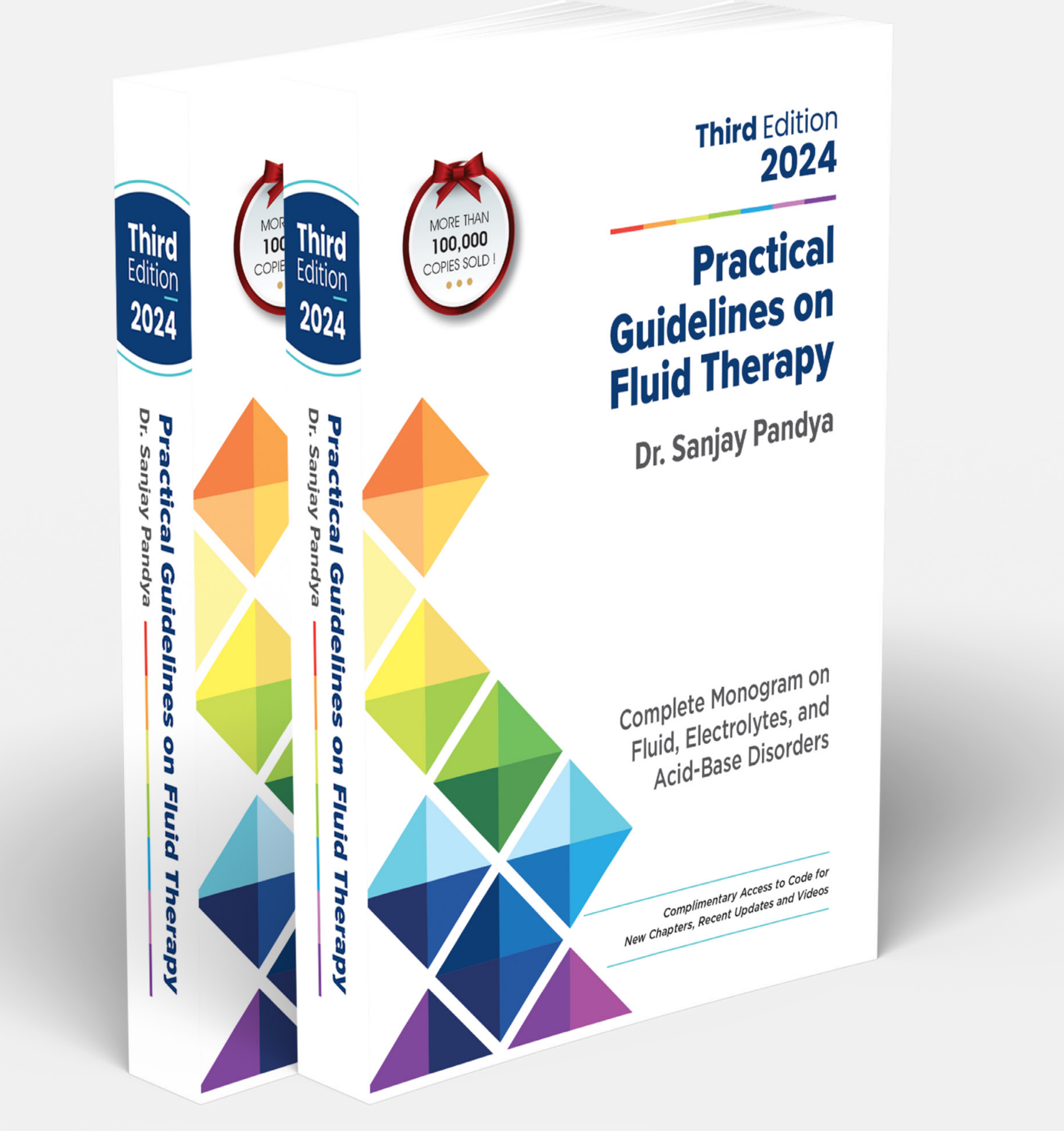
Chapter 51:

Maternal Changes and Fluid Management during Pregnancy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Maternal Changes and Fluid Management during Pregnancy

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During pregnancy, delivery, and in the postpartum period, administration of IV fluids may be required. It is essential to provide appropriate and timely fluid management whenever needed. This chapter aims to provide a basic understanding of the physiological changes that occur in the mother during pregnancy, as well as guidelines for fluid management in the cases of hyperemesis gravidarum and normal delivery.

MATERNAL PHYSIOLOGICAL CHANGES DURING PREGNANCY

Many physiological hemodynamic changes occur during pregnancy, starting just after conception and resolving within six weeks of delivery. An increase in weight gain during pregnancy is attributable to an increased size of the gravid uterus and breasts and an increase in blood volume and extravascular extracellular fluid [1]. Pregnancy-induced hemodynamic and cardiovascular changes ensure optimal growth and development of the fetus, and it also helps in the prevention of blood loss during delivery.

It is essential to understand changes in the circulatory system during pregnancy, such as an increase in cardiac output, retention of sodium and water leading to an expansion of blood volume, and a reduction in systemic vascular resistance and blood pressure. These physiological changes can significantly impact fluid management in pregnant patients, so understanding these changes can help in planning for fluid management in pregnant patients more efficiently.

A. Blood volume changes

Maternal plasma volume and red blood cell increase as early as the fourth week of pregnancy and peak at 28 to 34 weeks of gestation. During pregnancy, there is a retention of 900 to 1000 mEq of sodium and 6 to 8 liters of total body water, causing the expansion of total body volume [2–4].

The increased blood volume during pregnancy helps the body to meet the increased circulatory needs of the feto-placental unit, which are necessary to sustain the pregnancy. This increased blood volume also allows most women to tolerate significant blood loss during childbirth.

The maternal plasma volume increases by 40% to 50% during pregnancy. In comparison, the red cell volume only increases by 15% to 20%, resulting in hemodilution and a condition known as physiological anemia of pregnancy or relative anemia [5, 6].

B. Cardiovascular system changes

During pregnancy, cardiac output increases by 30% to 40%. The maximum increase usually occurs around 28–30 weeks of gestation [7]. This increase is due to both increased stroke volume and heart rate.

C. Blood pressure changes

Reduced systemic vascular resistance leads to a fall in blood pressure (BP) during pregnancy. The BP typically falls early in gestation and is usually 10 mmHg below baseline in the second trimester [2]. However, in the third trimester of pregnancy, systemic vascular resistance gradually increases, leading to a slow increase in blood pressure reaching nonpregnant levels by the end of the pregnancy [8].

D. Changes during labor and delivery

During labor and delivery, significant hemodynamic changes occur due to anxiety, exertion, pain, uterine contractions, uterine involution, and bleeding. During the first stage of labor, each uterine contraction displaces about 300 to 500 ml of blood into the general circulation and increases central blood volume by as much as 500 ml. As blood volume increases, the stroke volume of the heart also increases, leading to a 50% increase in cardiac output with each contraction.

In addition, maternal pushing efforts in the second stage of labor can further increase cardiac output. Immediately postpartum, cardiac output increases to 80 percent above pre-labor values due to significant autotransfusion associated with uterine involution.

Thus, the cardiac output can increase to 75% above its baseline level during labor and delivery. An increase in blood volume and cardiac output protects the mother from average blood loss of delivery (300–400 ml for a vaginal delivery and 500–800 ml for a cesarean section).

FLUID THERAPY IN HYPEREMESIS GRAVIDARUM

Nausea and vomiting of pregnancy (NVP) is the most frequent problem in the first trimester of pregnancy, which affects 50%–90% of all pregnant women [9, 10]. These symptoms are worse in the morning (but often persist throughout the day) and are usually limited to the first trimester of pregnancy.

Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting that affects a small percentage of pregnant women, ranging from 0.3% to 3%.

It can lead to significant weight loss, dehydration, ketoacidosis, hypokalemic metabolic alkalosis from the loss of gastric hydrochloric acid, and nutritional deficiencies [11–15].

Two serious nutritional deficiencies reported with hyperemesis in pregnancy are vitamin B1 (thiamine) deficiency (which can cause Wernicke's encephalopathy) and vitamin K^+ deficiency (which can cause maternal coagulopathy and fetal intracranial hemorrhage) [16].

Hyperemesis gravidarum is the major reason for hospitalization during the first half of pregnancy and remains the second leading cause of hospitalization throughout pregnancy [17, 18].

Management

Management of hyperemesis gravidarum includes adequate hydration, antiemetic medications, electrolyte replacement, vitamin supplementation, and dietary management [19, 20]. Intravenous hydration is an essential intervention aimed at fluid resuscitation and correcting fluid deficit, ketones, electrolytes deficit (primarily hypokalemia), and acid-base balance [21]. In addition, as pregnant women are in a catabolic condition, sufficient caloric requirements must be administered [22].

1. Indications of IV fluids

Common indications of IV fluid administration in hyperemesis gravidarum are [23, 24]:

- Persistent vomiting (three or more times per 24 hours) despite antiemetic medical therapy.
- 5% or more weight loss of prepregnancy weight.
- Severe dehydration with the presence of signs and symptoms due to significant fluid loss such as fatigue, dizziness, decreased skin turgor, postural changes in blood pressure and pulse, ketonuria, electrolyte imbalance, acid-base abnormality like hypochloremic metabolic alkalosis, increased hematocrit, increased BUN to creatinine ratio and abnormal urine specific gravity.

2. Outpatient vs. inpatient IV hydration

Ambulatory (outpatient) intravenous hydration is the recommended first-line treatment for patients with severe or persistent nausea and vomiting. Multiple studies have found this treatment option to be as effective as inpatient care [25, 26].

Hospitalization is recommended if vomiting persists even after rehydration and outpatient management fails [27].

3. Selection of IV fluids

Normal saline (NS) and Ringer's lactate are the mainstay of the management of dehydration and are equally effective in treating complications of hyperemesis gravidarum [28, 29]. Usually, Ringer's lactate (RL) is preferred for the initial aggressive rehydration, and normal saline is used for the subsequent slower rehydration [30].

Why is Ringer's lactate preferred for the initial aggressive rehydration and in patients of HG with severe hyponatremia?

The speed at which one rehydrates depends on the severity of their dehydration. In patients of hyperemesis gravidarum with severe dehydration, 2 liters of Ringer's lactate is infused rapidly initially (first 1 liter RL over 2 hours followed by second 1-liter RL over 4 hours). In severe hyponatremia, avoid rapid administration of a large volume of high sodium containing normal saline (sodium 154 mEq/L), as it can lead to rapid correction of sodium levels and may cause central pontine myelinolysis [30].

Therefore in symptomatic and severe hyponatremia (serum sodium <120 mEq/L), choose low sodium containing Ringer's lactate (130 mEq/L sodium) which carries lower risk of rapid correction of hyponatremia.

Why is normal saline preferred for the subsequently slow rehydration in and in patients of HG with less severe hyponatremia associated with hypochloremia?

For hospitalized women with hyperemesis gravidarum who are hypovolemic with minimal symptoms of hyponatremia and have serum sodium levels >120 mEq/L (low risk of rapid correction) and hypochloremia, normal saline is an appropriate choice for rehydration. Normal saline containing 154 mEq/L sodium and chloride is a preferred fluid in HG for hydration because it corrects vomiting-induced hypochloremia, hyponatremia, hypokalemia, and metabolic alkalosis effectively [31].

If hypokalemic, the woman may require potassium supplementation [12, 32]. Usually, 20 mEq/L of potassium chloride is added to either normal saline or half-normal saline (depending on the serum sodium status) and infused slowly (over 6 to 8 hours) to correct hypokalemia.

In severe hypokalemia, consider potassium replacement using one liter of normal saline with 40 mEq potassium chloride to be infused over 4–6 hours. 10 mEq of potassium per hour is a safe infusion rate if urine output is adequate.

4. Role of dextrose solutions

Avoid dextrose-containing IV fluids for the initial fluid replacement, but it may be beneficial for the subsequent IV fluid infusion. Two reasons to avoid dextrose containing IV fluids for the initial fluid replacement are [33]:

- Risk of Wernicke's encephalopathy: As thiamine (vitamin B1) deficiency occurs in about 60% of hyperemesis gravidarum patients [34], dextrose-containing IV fluids can precipitate Wernicke's encephalopathy in such patients [10]. Supplement 100 mg of thiamine intravenously with the initial IV fluid on the first day and another 100 mg daily for the next two or three days to prevent Wernicke's encephalopathy [25, 33, 35].
- Risk of worsening of hypokalemia: Hypokalemia is a common electrolyte abnormality in hyperemesis gravidarum [16]. It is recommended to avoid using dextrose-containing solutions for initial fluid replacement, as dextrose administration stimulates insulin release, which can cause extracellular potassium to be shifted into cells and worsen hypokalemia.

After thiamine supplementation and supplementing potassium, maintain hydration with the dextrose-based solution as it fulfills the caloric requirement and helps in faster improvement of nausea [36]. In addition, evidence suggests better improvement with dextrose saline than normal saline in moderate-severe cases [37]. Finally, select 10% dextrose to provide nutritional supplementation rather than the low-calorie-containing 5% solution [38].

Continue administering IV hydration until ketosis and vitamin deficiencies are corrected, and the patient is able to tolerate oral fluids. Afterward, check and address any associated magnesium, calcium, and phosphorus deficits.

To effectively address fluid deficit with hyponatremia and hypokalemia, it is crucial to monitor the input-output chart and check the blood urea and serum electrolyte levels daily [25]. This will allow for the accurate selection of the appropriate IV fluids necessary for treatment.

FLUID THERAPY DURING NORMAL LABOR AND VAGINAL DELIVERY

Labor is a period of prolonged and vigorous exercise for pregnant mothers. During labor, effective skeletal and smooth muscle contractions require increased energy demand. Glucose is an essential source of maternal energy, which plays an important part in the improvement of muscle performance and overcoming fatigue. Depletion of glycogen stores and fat metabolism to meet glucose demands may cause ketonemia, hypoglycemia, and acidosis. An adequate resource of glucose is needed to maintain exercise tolerance and muscle efficiency during labor. Dehydration adversely affects exercise performance and may be a factor contributing to a longer duration of labor. Providing adequate dextrose and fluids to pregnant mothers during labor can help to provide the necessary energy and hydration they need and may also lead to a faster labor process, shorter labor duration, and potentially a reduced need for oxytocin and cesarean delivery [39, 40]. To assess the hydration status, it is important to monitor urinary output and the presence or absence of ketonuria [41].

A. Oral liquid intake

Previously, the policy during active labor was "nil by mouth," or restriction of oral intake. This policy was based on the concern that a woman may require general anesthesia for an emergency cesarean section and inhale stomach contents during surgery, leading to aspiration pneumonia [42]. However, the risk of aspiration pneumonia is very low [43], and restricting oral intake can cause dehydration and ketosis [44]. Therefore, this policy is not necessary and may cause harm to the woman [44].

Women with low complication risks and at low risk of cesarean section delivery are allowed and encouraged to consume moderate amounts of clear liquids orally during labor [45–47]. However, to avoid aspiration during uncomplicated labor, it is more important to consider how much suspended particulate matter the fluid ingested contains rather than the volume of fluid permitted to be consumed [45].

During labor, it is necessary to restrict oral intake in patients who are at high risk of aspiration (e.g., morbid obesity, diabetes mellitus, and difficult airway) or those who may need a cesarean section [45].

B. Oral solid food intake

Avoiding particulate-containing fluids and solid food during active labor and delivery is the standard practice and a recommendation by the American College of Obstetricians and Gynecologists (2009) and the American Society of Anesthesiologists Task Force on Obstetric Anesthesia (2016) [45–47]. This recommendation is because gastric emptying time is remarkably prolonged during labor.

However, the incidence of aspiration is low with current obstetric anesthesia techniques in recent literature. Therefore, solid food restriction in women at low risk of requiring general anesthesia is questioned [42, 48, 49].

Cochrane review (2013) found no evidence to support restriction to eating or drinking in women at low risk of requiring anesthesia for Cesarean section [50]. However, a recent systematic review (Ciardulli et al. 2017) of 10 randomized trials in women with a low-risk singleton (one fetus) pregnancies found that less restrictive policies resulted in a slightly shorter duration of labor [51].

C. Parenteral fluids in normal labor

During normal labor, intravenous fluids are usually administered for proper hydration and to prevent prolonged labor. But as per current evidence from the Cochrane database of systematic reviews (2013), the World Health Organization (2014), and the American College of Obstetricians and Gynecologists (2019), continuous IV fluid infusion is not routinely recommended in normal labor [39, 52].

Regardless of solution type, possible harmful effects to mother and newborn due to the administration of intravenous fluids during labor are:

1. Discomfort, stress, and restriction in freedom of movement.
2. Peripheral swelling and increased risk of fluid overload due to excessive IV fluids.
3. Postpartum breast swelling and feeding issues due to the large volume of IV fluids infusion [53].
4. Fetal volume expansion causes a bloated newborn at birth and greater weight loss of the newborn after birth [54, 55].

Moreover, oral food and liquids are more effective than intravenous fluids in providing energy and nutrition for the increased demand during labor [50]. Thus, instead of administering intravenous fluids to all women during labor, they should be given only to selected patients, considering their limitations and drawbacks.

Conclusion: During normal labor, avoid the "nil by mouth" policy and do not administer intravenous fluids routinely to prevent dehydration and ketosis [39, 52].

1. Indications of IV fluids during labor

When oral fluid intake is restricted, administering IV fluids in a moderate amount shortens the course of labor [39]. So the administration of IV fluid is indicated in selected pregnant mothers.

Common indications for intravenous fluid administration during labor include:

- High-risk pregnancies or restricted oral intake because of the possible need for cesarean delivery.
- Women who develop ketosis in labor [39].
- Following epidural or spinal anesthesia for cesarean delivery to prevent or treat hypotension [56].
- Infusion of oxytocin for induction or augmentation of labor.
- Need to administer intravenous fluids for other clinical reasons such as nausea, vomiting, diarrhea, maternal exhaustion, prolonged labor, blood volume loss, and administration of antibiotics or other medications [57].

2. Type and volume of IV fluids

When IV fluids are indicated, the selection of the type, the volume, and the infusion rate of IV fluid differ on the clinical status of individual women and the anticipated duration of labor [39].

For nulliparous women who are not allowed oral intake during labor, the infusion of dextrose solution significantly reduces the total labor length without increasing the complication rate [40, 58–60].

Because of its cost-effectiveness, safety, and advantages, dextrose should be the default solute for IV fluids during labor [59, 61]. Maintenance intravenous fluid usually administered is 5% dextrose in 0.45 percent saline, normal saline, or Ringer's lactate solution [62]. Avoid administering sodium-free 5% dextrose solution because it may cause maternal and neonatal hyponatremia and increase maternal and newborn morbidity [39].

Rate of infusion: IV fluid administration at a rate of 250 ml/hour, rather than 125 ml/hour, is associated with a shorter duration of labor and lesser need for cesarean section delivery. This data support increased hydration among nulliparous women in labor when oral intake is restricted [63].

PREOPERATIVE ORAL INTAKE

A. Liquid intake

The uncomplicated patient undergoing elective cesarean delivery may have clear liquids up to 2 hours before induction of anesthesia (American Society of Anesthesiologists (ASA) recommendation 2016) [45]. Consuming high-calorie carbohydrate drinks up to two hours before surgery can reduce preoperative thirst, hunger, anxiety, and the risk of dehydration in patients undergoing abdominal surgery [64, 65].

In pregnant women with a higher risk for aspiration during labor (e.g., morbid obesity, diabetes mellitus, and difficult airway), the recommendation is to restrict oral liquid intake for 6 or more hours, determined on a case-by-case basis [45].

B. Solid food intake

During elective surgery (e.g., planned cesarean delivery or postpartum tubal ligation) recommended fasting period for solid food is 6 to 8 hours [45].

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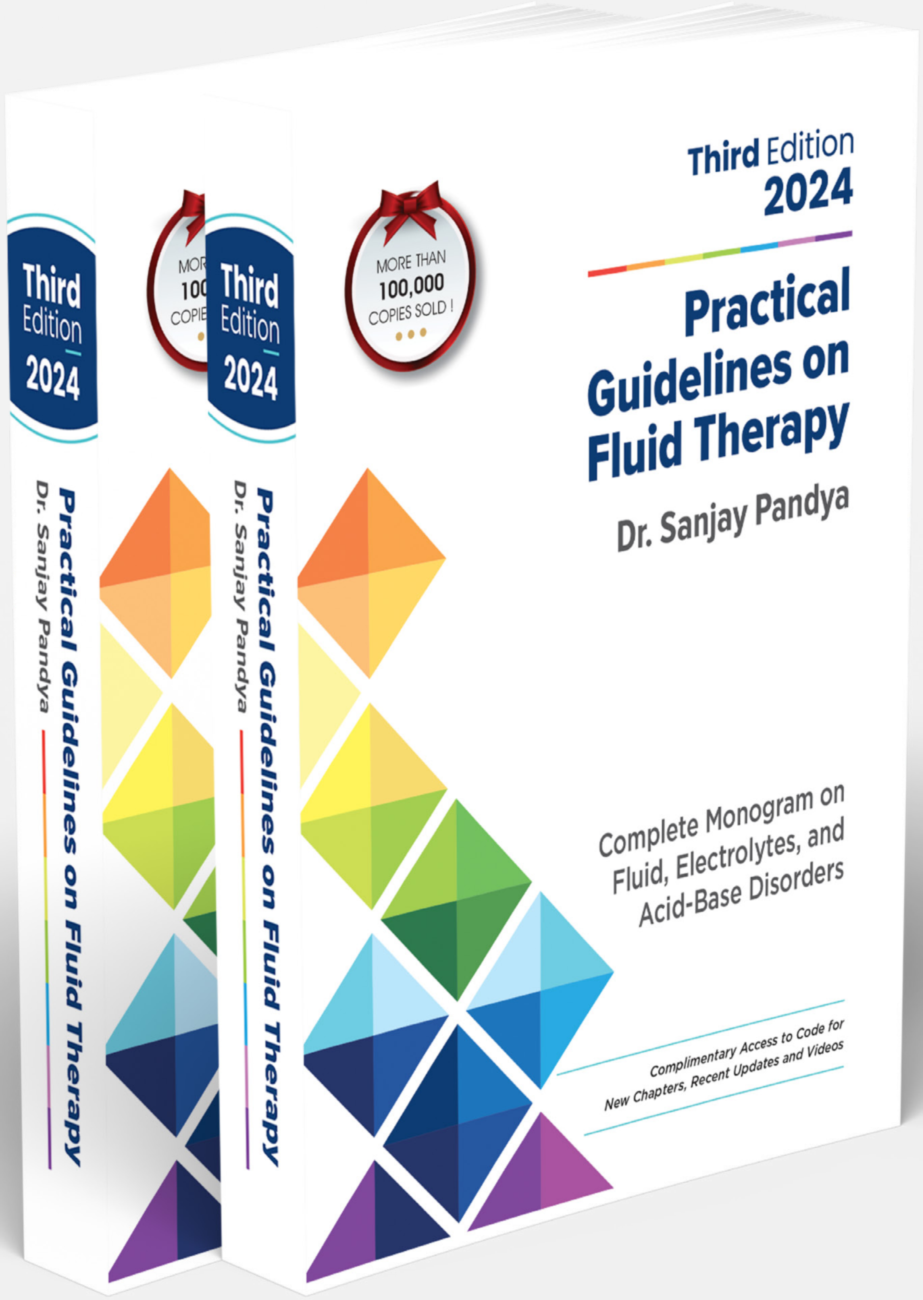
Chapter 52:

Fluid Management for Cesarean Delivery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Spinal anesthesia is the most common type of anesthesia used in cesarean sections [1].

Maternal hypotension is the most common complication of spinal anesthesia for cesarean delivery. Maternal hypotension is defined as systolic blood pressure (SBP) <90 mmHg or a reduction in mean arterial blood pressure >30% fall from baseline [2].

The incidence of maternal hypotension during spinal anesthesia for elective cesarean delivery is much higher (70–80%) [3] as compared to the incidence of hypotension caused by spinal anesthesia in nonpregnant women (about 33%) [4].

Mechanism of maternal hypotension: Spinal anesthesia blocks the sympathetic nerve fibers innervating smooth muscles of arteries and veins, which causes reduced peripheral vascular resistance and vasodilatation. Vasodilatation in the lower part of the body is the crucial mechanism of the development of hypotension due to spinal anesthesia in uncomplicated pregnancy [5].

Consequences of maternal hypotension: Maternal hypotension after spinal anesthesia for cesarean section causes both maternal and fetal/neonatal adverse effects [6]. Spinal hypotension can result in maternal nausea, vomiting, and dizziness due to a reduction in cerebral perfusion, which induces transient brainstem ischemia [7]. In addition, treatment of spinal hypotension can cause iatrogenic pulmonary edema or severe maternal hypertension. Severe and sustained hypotension can decrease uteroplacental perfusion, which can cause fetal hypoxia, acidosis, and neonatal depression [8].

MANAGEMENT OF HYPOTENSION DURING CESAREAN DELIVERY

The goal of management is to optimize maternal, uterine, and fetal perfusion, which is crucial for the mother's safety and the baby's wellbeing.

Major steps in treating spinal hypotension are fluid loading, vasopressor, and non-pharmacological measures. Combinations of interventions will be more effective than single ones [9].

The goal of blood pressure

Treatment aims to maintain systolic blood pressure ≥100 mmHg or ≥90% of an accurately measured baseline blood pressure [10, 11].

A. Fluid loading

Before the initiation of spinal anesthesia, it is important for the patient to have large-diameter intravenous access (preferably 16 or 18 gauge) in place. This will allow for the rapid administration of fluids, medications, and blood products if necessary.

The two most important determinants for the optimal and effective treatment of spinal hypotension are: (1) The type of fluid (crystalloid compared with colloid solutions) and, (2) The timing of administration [given before spinal anesthesia (preloading) or given immediately after spinal block placement (co-loading) as rapid infusions.

1. Preloading

Preloading is a method where IV fluid is administered immediately before spinal anesthesia to reduce post-spinal hypotension (PSH).

Crystalloid preloading: Rapid administration of 10–20 mL/kg of intravenous Ringer's lactate just 15–20 minutes before spinal anesthesia was previously a routine practice to minimize hypotension resulting from sympathetic blockade. But fluid preloading with crystalloid is clinically ineffective due to its rapid redistribution and therefore is currently not recommended before spinal anesthesia [9, 12, 13].

Colloid preloading: In contrast to crystalloid preloading, colloid preloading significantly reduces hypotension and improves maternal hemodynamics [9, 14].

As preloading is not superior to co-loading (irrespective of the type of IV solution used), one should not waste significant time in administering a predetermined IV fluid volume and consequently delay spinal anesthesia initiation [15].

2. Co-loading

In co-loading, IV fluids are rapidly administered and started simultaneously with spinal anesthesia to reduce post-spinal hypotension. Using co-loading protocols is less time consuming with better (or at least similar) effects than preloading [16].

Co-loading is a more rational and physiological approach. In fluid co-loading, IV fluid administration coincides precisely with the time of the maximal vasodilatory effect of spinal anesthesia and thereby compensates for the "relative hypovolemia" and prevents post-spinal hypotension [17].

Crystalloid co-loading: A balanced electrolyte solution (e.g., Ringer's lactate solution) is the most commonly used intravenous fluid for bolus administration. Usually, a bolus of about 10–15 ml per kg or 500 to 1000 mL of Ringer's lactate is infused as fast as possible in fluid co-loading.

Use dextrose free IV fluids for crystalloid co-loading because it avoids maternal hyperglycemia. The immediate effect of maternal hyperglycemia is fetal hyperglycemia, but it may cause neonatal hypoglycemia after delivery. When dextrose containing IV fluid is administered to the mother before delivery, glucose crosses the placental barrier and can result in fetal hyperglycemia and and hyperinsulinemia. After delivery, the glucose supply is ceased, but neonatal insulin levels are still elevated, which causes neonatal hypoglycemia [18].

The volume of fluid given during spinal anesthesia may vary depending on the patient's underlying co-morbidities and their current volume status, with a smaller volume typically being given to patients with severe preeclampsia.

Crystalloid co-loading is more effective than crystalloid preloading in preventing hypotension during spinal anesthesia for elective cesarean delivery [19–22]. Additionally, crystalloid co-loading is similar in effectiveness to colloid preloading [23].

Colloid co-loading: For colloid co-loading third generation colloids such as tetrastarch (Hydroxyethyl starch 130/0.4) seem safer than other colloids [24]. Colloid co-loading is not superior to colloid preloading [17].

Both crystalloid and colloid co-loading are equally effective in decreasing the incidence of spinal hypotension in cesarean delivery [21, 25]. However, the volume needed for colloid co-loading is less than that required for crystalloid co-loading [23].

Because of less adverse effects, lesser cost, ready availability, and restricted or second line usage of colloids in most studies [26], current literature recommends the use of crystalloids than colloids co-loading in cesarean delivery [27].

Factors affecting fluid requirements: Total requirement of intravenous fluids (crystalloids) during and after cesarean delivery varies considerably but is usually 2 to 3 liters. The requirement of fluid volume may be higher in patients with sepsis syndrome, vomiting, prolonged labor without adequate fluid intake, and increased blood loss.

In patients with preeclampsia, spinal anesthesia tends to cause less hypotension than it does in normal pregnant women. Therefore, it is recommended to use mild to moderate intravascular volume loading during spinal anesthesia in patients with preeclampsia.

The loading of a large volume of fluid carries the risk of pulmonary edema in preeclampsia [19].

B. Vasopressors

Vasopressor therapy is a crucial component in minimizing spinal hypotension. Fluid loading protocols alone are not usually sufficient to achieve reasonable control in post-spinal hypotension [16]. Besides crystalloid or colloid co-loading, a significant proportion of patients require vasopressors to control spinal hypotension [28].

Vasopressor treatment aims to restore systemic vascular resistance. Alpha-adrenergic agonist drugs are the most appropriate agents to treat or prevent hypotension following spinal anesthesia [11]. In addition, prophylactic vasopressors are superior in preventing adverse neonatal outcomes compared to reactive treatment [29].

Phenylephrine and ephedrine are the two most widely used and recommended vasoconstrictor agents in treating spinal hypotension [15]. Phenylephrine is a synthetic selective direct alpha-adrenergic agonist. Ephedrine is a synthetic mixed adrenergic agonist. Ephedrine is a stimulant that directly activates alpha and beta-adrenergic receptors and indirectly stimulates the release of endogenously stored norepinephrine. Recently, even norepinephrine (noradrenaline) has been found to be helpful in preventing and treating spinal hypotension during cesarean delivery.

1. Phenylephrine

A combined approach using titrated phenylephrine with crystalloid co-loading is probably the best option for the management of hypotension during spinal anesthesia for cesarean section [6, 21]. Phenylephrine infusions co-administered with crystalloid has shown to eliminate the likelihood of spinal hypotension [30].

Pharmacology: Phenylephrine is a drug that acts selectively on the alpha-1 adrenergic receptors found on the vascular smooth muscle cells in blood vessels, resulting in vasoconstriction. It is a potent agent that increases total peripheral vascular resistance and increases both systolic and diastolic blood pressure. The onset of action is <1 minute, and its duration of effect is short lasting (15 to 20 minutes). At higher doses, phenylephrine can cause bradycardia due to the activation of baroreceptors, which can lead to a reduction in maternal cardiac output [31].

Preparation: Injection phenylephrine, available as a 1 ml ampoule, contains 10 mg of phenylephrine.

Method of administration (bolus vs. infusion)

In the treatment of spinal hypotension, prophylactic phenylephrine infusion is superior to bolus administration because of the lower incidence of intraoperative nausea and vomiting [32, 33]. An international consensus statement for the management of spinal hypotension by AAGBI (2018) recommends prophylactic phenylephrine infusion as the first line of management [11].

Dose: To prepare an infusion, add 1 ml (10 mg) of phenylephrine solution in 100 ml of normal saline. Each ml of this infusion will provide 100 mcg of phenylephrine (100 mcg/ml solution).

a. **IV bolus:** A commonly used dose of a prophylactic bolus of IV phenylephrine is 50 to 100 mcg (0.5 to 1 ml). Repeat the dose every 2 to 5 minutes as required, but do not give more than a total dose of 200 micrograms (mcg).

b. **IV infusion:** Currently recommended dose of phenylephrine infusion is 25–50 mcg/min. (0.25 to 0.5 ml/min) [11, 16] Prophylactic phenylephrine infusion is started with an infusion pump as soon as the spinal anesthesia is given. The dose is titrated according to maternal systolic blood pressure response and pulse rate.

   A higher incidence of post-spinal hypotension occurs with the lower dose (25 mcg/min), and a higher incidence of reactive hypertension and bradycardia occurs with the higher dose (50 mcg/min) [31, 34].

c. **IV bolus followed by infusion:** When phenylephrine is infused after spinal anesthesia, there will be a delay in achieving adequate blood pressure levels. However, an initial phenylephrine bolus immediately after the spinal anesthesia, followed by a phenylephrine infusion, will maintain blood pressure without adverse effects [5].

2. Ephedrine

Ephedrine is a sympathomimetic drug that stimulates both alpha and beta-adrenergic receptors. As a result, it stimulates the heart rate, increases cardiac output, and variably increases peripheral resistance, leading to an increase in blood pressure.

Previously, ephedrine was the first-line treatment for spinal hypotension. But the trend to use ephedrine in the treatment of post-spinal anesthesia hypotension is decreasing because:

- Repeated administration of ephedrine diminishes its vasoconstrictive effect [35].
- Delayed onset of action of ephedrine may result in a longer period of hypotension than phenylephrine.

- The relatively long duration of the effect of ephedrine makes accurate titration of blood pressure difficult [36].
- Ephedrine may increase the risk of fetal acidosis by crossing the placenta to a greater extent [37].

Currently, ephedrine is preferred to treat spinal hypotension in a pregnant patient with bradycardia, as it typically increases heart rate.

The commonly used dose of ephedrine is 5 to 10 mg IV boluses or 1 to 5 mg/min IV infusion.

3. Phenylephrine versus ephedrine

Ephedrine was previously the first-line therapy for parturients with spinal hypotension [38]. But phenylephrine is currently vasopressor of choice in the treatment of spinal hypotension in the absence of maternal bradycardia [39–41]. Reflex bradycardia and decreased cardiac output are the primary concerns associated with phenylephrine.

As compared to ephedrine, phenylephrine is preferred and superior because of its faster onset [42], ease to titrate, better preservation of uterine blood flow, does not cause or worsen maternal tachycardia [43, 44], less reactive hypertension [45], less incidence of fetal acidosis [46], and less maternal nausea and vomiting [47, 48].

However, ephedrine may be more beneficial in patients with bradycardia, compromised cardiac functions, uteroplacental insufficiency, and pre-eclampsia [16].

Vasopressor selection based on maternal heart rate:

- Hypotension and tachycardia: This is the usual response to spinal anesthesia, and phenylephrine is a preferred vasoconstrictor agent in treatment.
- Hypotension and bradycardia: This is the unusual response that resembles a vagal reaction; rather than 'appropriate' tachycardia and vasoconstriction. Ephedrine is a preferred vasoconstrictor agent for spinal hypotension associated with bradycardia [40].

4. Norepinephrine as vasopressor

Norepinephrine (NE, noradrenalin) is recently introduced to prevent and treat spinal hypotension during cesarean delivery [49, 50]. Norepinephrine (NE) is a potent vasopressor having both alpha-adrenergic agonistic activity, and weak beta-adrenergic agonistic activity. NE has minimal cardiac depressant effect [51]. NE has a similar effect to phenylephrine in maintaining blood pressure but may be associated with higher heart rates (closer to baseline), and greater cardiac output [52, 53].

Because of beneficial cardiac effects and potency, NE may be preferred in mothers with low baseline heart rates or poor cardiac function, where phenylephrine is relatively contraindicated [51].

More research is needed to evaluate the safety and efficacy of norepinephrine before its routine use in obstetric patients [51, 54]. Table 52.1 summarizes all vasopressors used in spinal hypotension during cesarean delivery.

C. Non-pharmacological measures

In the supine position, the gravid uterus compresses the maternal abdominal aorta and inferior vena cava, which decreases cardiac output [55]. Positioning protocols for the prevention of post-spinal hypotension are targeted to relieve aortocaval compression imparted by the gravid uterus and increase venous return [16]. Left lateral uterine displacement with 15° table tilt reduces inferior vena cava compression and is routinely recommended in addition to other measures [11, 56, 57].

POSTOPERATIVE CARE AFTER CESAREAN DELIVERY

Early oral intake

After cesarean delivery, fluids or food is traditionally avoided until bowel functions return (confirmed by bowel sounds or passage of flatus or stools). But in uncomplicated cesarean delivery, evidences to justify the restriction of oral fluids or food is lacking.

Current evidence suggests that early oral intake (within six hours of delivery) may have several benefits for postpartum care. These benefits include promoting the return of bowel function (through the stimulation of the gastrocolic reflex), encouraging early ambulation, reducing the duration of intravenous fluid administration, decreasing the risk of sepsis, shortening the time to breastfeeding, decreasing the length of hospital stay, and reducing the cost of hospitalization [58–61].

Nausea and vomiting after cesarean delivery can delay early oral intake. In the management of postoperative nausea

Table 52.1 Vasopressors in spinal hypotension during cesarean delivery

Vasopressor	Phenylephrine	Ephedrine	Norepinephrine (noradrenaline)
Mechanism of action	Selective direct α 1 receptor agonist	Direct α and β agonist and indirect release of norepinephrine	Direct α 1 and β 1 agonist
Arterial vasoconstriction	Potent	Less potent	Potent
Chronotropic effect	Negative	Positive	Positive
Maternal heart rate	Reflex bradycardia	Tachycardia	Increased
Cardiac output	Decrease	Increase	Modest increase
Onset of action	Faster	Slower	Immediate
Duration of action	Short-acting (15 to 20 minutes)	Relatively long duration (about 60 min), so longer period of hypotension	Very short (1 to 2 minutes)
Advantage	No maternal tachycardia, better titratability	No maternal bradycardia	Less negative effects on heart rate and cardiac output
Selection	Currently preferred vasopressor in post-spinal hypotension. Preferred in maternal tachycardia	Preferred in maternal bradycardia in post-spinal hypotension	Beneficial effects in mothers with bradycardia and compromised cardiac function in recent studies
Strength of injectable solution and dilution	10 mg/mL (1 mL diluted in 100 ml of normal saline equals 100 mcg/mL)	30 mg/mL, 50 mg/mL (1 mL diluted in 10 ml of normal saline equals 3 mg/mL or 5 mg/mL)	1mg/mL (2 mL diluted in 500 ml of D5W or D5NS equals 4 mcg/mL)
Commonly used doses	50 to 100 mcg IV bolus or 25 to 100 mcg/min IV infusion	5 to 10 mg IV boluses or 1 to 5 mg/min IV infusion	Further studies are required before its routine use

and vomiting (PONV), the combination of anti-emetics is more effective than monotherapy [62].

During cesarean delivery, intraoperative nausea and vomiting (IONV) are common [7]. Measures to reduce IONV during cesarean are the prevention of hypotension with liberal perioperative administration of IV fluids, maintaining normal blood pressure with prophylactic use of vasopressors (i.e., phenylephrine or ephedrine), administration of anti-emetics (metoclopramide and ondansetron) and minimizing visceral manipulation (e.g., uterine exteriorization) [63, 64].

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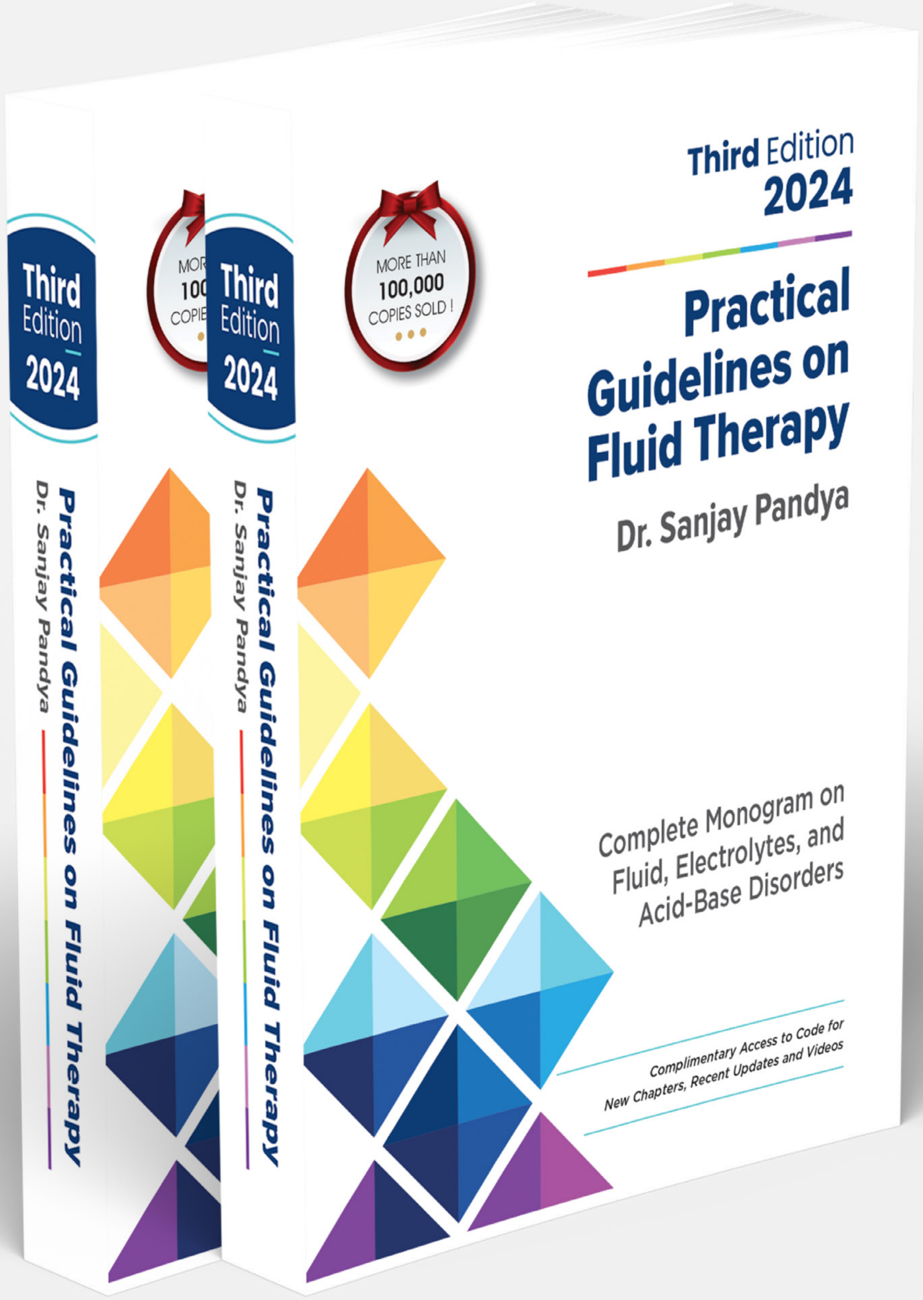
Chapter 53:

Fluid Management in Preeclampsia and Postpartum Hemorrhage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Fluid Management in Preeclampsia and Postpartum Hemorrhage

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Preeclampsia and postpartum hemorrhage are two common problems that need meticulous fluid management.

FLUID MANAGEMENT IN PREECLAMPSIA

Preeclampsia (PE) is a condition that is characterized by hypertension and significant proteinuria that occurs after 20 weeks of pregnancy.

One of the common clinical symptoms of preeclampsia is generalized edema. However, it's important to note that peripheral edema can occur in normal pregnancies. Therefore, one should suspect preeclampsia when weight gain is sudden and rapid (> 2.3 kg/week).

Fluid management for the patient with preeclampsia presents a challenge for the obstetrician as there are considerable controversies and data on the ideal fluid strategy are limited and insufficient [1].

In preeclampsia, two paradoxical findings, intravascular volume depletion, and increased extracellular fluid volume, lead to confusion and different opinions regarding optimal fluid management.

Excessive administration of IV fluids and mobilization of fluid sequestered in the extravascular space into the vascular space carries a high risk of pulmonary edema in preeclampsia [2].

Fluid management should be customized to the specific clinical situation and closely monitored to achieve optimal fluid balance. Fluid management aims to maintain circulating volume and preserve kidney function while minimizing the risk of pulmonary edema.

A. Basic principles of fluid balance in PE [1, 3, 4]

- As patients with preeclampsia are edematous, it is important to carefully infuse optimal IV fluids with the aim of restricting fluid to avoid pulmonary edema.
- Aggressive fluid therapy carries a risk of pulmonary edema; therefore, fluid management requires frequent

clinical assessment and meticulous attention. Record fluid balance carefully.

- For precise infusion of intravenous fluids, use a volumetric infusion pump.
- Replace obvious blood loss during delivery.
- Pulmonary edema carries a higher risk of death compared to oliguric renal failure. Therefore, it is important to avoid the overuse of crystalloid solutions to treat postpartum hemorrhage (PPH) in patients with preeclampsia.
- Avoiding IV fluids preloads before spinal anesthesia.
- To maintain optimal fluid balance, restrict fluid intake to a maximum of 40 ml per hour plus the previous hour's urine output, up to a total of 80 ml per hour or 1 mL/kg/hr. The type of fluids preferred are balanced crystalloids (Hartmann's solution, Ringer's lactate, or PlasmaLyte).
- As oliguria is common with severe preeclampsia, maintain fluid restriction until there is a postpartum diuresis.
- Administer infused drugs in concentrated solutions to avoid excessive fluid volume administration.
- Do not chase an increased urine output that follows delivery, as it carries a risk of volume overload.
- Insert the indwelling catheter and measure urine output hourly with a urometer.
- In preeclampsia, a central line is usually only indicated if there is significant obstetric bleeding or severe heart dysfunction. Before insertion of the central line, always check the coagulation profile and platelet count because Preeclampsia is often complicated by HELLP syndrome.
- Monitor SpO_2 closely. Fluid overload is the most likely cause of a decrease in oxygen saturation. Deterioration of SpO_2 below 95% may indicate impending pulmonary edema. Use diuretics only when the diagnosis of pulmonary edema is confirmed.

B. Antenatal fluid management in PE

Careful fluid balance is essential. In preeclampsia, it is important to restrict intravenous and oral fluid intake in order to prevent fluid overload and pulmonary edema. When the administration of syntocinon (oxytocin) is indicated, it is advisable to use a high-concentration infusion (30 IU in 500 mL) or, for even more concentrated solutions, dilute it in just 50 mL and deliver it using an infusion pump to prevent fluid overload [4].

Women with preeclampsia have an increased risk of requiring a cesarean delivery. Therefore, keeping them on a "nil by mouth" or limiting oral fluid intake to 30 ml per hour or less is recommended to minimize the risk of complications during surgery [3, 5].

In the antepartum period, furosemide is used only to treat patients with severe preeclampsia complicated by pulmonary edema [6].

C. Fluid management during labor in PE

IV fluid in PE: to use or not?

Fluid management in preeclampsia is complex, and there is limited and insufficient data on the ideal fluid strategy for women with this condition [1].

1. Volume restriction

Acute pulmonary edema is a common cause of death in women with preeclampsia and often leads to admission to the intensive care unit [7]. Pulmonary edema kills, but oliguria and renal failure do not, so administer fluid cautiously in preeclampsia.

A fluid restriction regimen is associated with lower rates of pulmonary edema and good maternal outcome [8, 9]. Multiple recent guidelines recommend against plasma volume expansion (NICE, SOGC, SOMANZ) and recommend fluid restriction (NICE, GAIN, CMQCC, SOGC) [9–13]. For women with severe preeclampsia and without any fluid losses, it is recommended to restrict total fluid intake to 80 ml/hour, which includes oral, drug, and intravenous fluids [9, 10].

2. Volume expansion

Women with preeclampsia have reduced plasma volume and are usually oliguric. Therefore, fluid restriction is generally recommended in preeclampsia but may not be appropriate for all women. Achieving proper fluid balance before delivery is essential [14]. Intravenous fluid administration may be used judiciously as maintenance therapy or for resuscitation [15]. Replacement therapy is administered according to an estimated deficit and is usually transfused rapidly.

Common indications of fluid administration in preeclampsia are the following [15, 16]:

- As a vehicle to administered IV labetalol or IV hydralazine for the adequate and more reliable control of severe hypertension.
- To replace ongoing blood and fluid loss.
- As a vehicle for administering agents for induction/augmentation of labor and anticonvulsant medication.
- Maintenance therapy. The preeclamptic woman who is fasting may need intravenous fluid to maintain hydration. Maintenance fluid is commonly given intravenously slowly over 24 hours, and its volume should match the urinary output combined with the insensible loss [15].
- Oliguria due to suspected or confirmed intravascular volume deficit [17].

3. The choice of IV fluids: colloids vs. crystalloids

The theoretical benefits of colloids are that they remain in the vascular compartment longer than crystalloids, and a smaller volume of solution is required for volume expansion. However, most of the previous comparative trials of colloids and crystalloids excluded pregnant women in their studies, so choosing between these two solutions during labor is controversial [18].

There is no evidence in the literature of general critical care to support the use of colloids over crystalloids for fluid resuscitation, and current studies favor the use of crystalloids over colloids [18–20].

D. Fluid during spinal anesthesia in PE

Spinal or epidural anesthesia is generally considered better and safer for cesarean section in preeclampsia due to improved hemodynamic stability and better outcomes for newborns [21].

Women with preeclampsia develop less hypotension after spinal anesthesia than healthy women [22–24].

General anesthesia carries a higher risk compared to neuraxial anesthesia in preeclampsia. Some of the significant risks associated with general anesthesia include the risk of aspiration [25] and an abrupt, severe increase in hypertension during intubation and extubation [5, 26]. Such sudden, severe hypertension carries a risk of hypertensive crisis and stroke [27].

Additionally, preeclampsia-associated tissue edema can lead to narrowing around the larynx, making endotracheal intubation difficult [28].

A prophylactically or routine fixed intravenous fluid preload bolus should never be administered before initiating neuraxial anesthesia in preeclampsia [4, 5, 9].

Administer crystalloid/colloid carefully for co-loading. As a general rule, 500 mL to 1000 mL is sufficient unless the fluids are being used to replace blood loss [3, 5].

Phenylephrine is the optimal first-line vasopressor to reverse spinal hypotension in preeclampsia. However, prophylactic vasopressor infusion in preeclampsia is not usually required, and the dose of phenylephrine to treat hypotension may be lower than in healthy women.

It is essential to monitor the blood pressure carefully during cesarean section, as the fetus may not tolerate sudden decreases in blood pressure well. If necessary, a low dose of phenylephrine can be administered to treat spinal hypotension [22, 29].

E. Postpartum fluid management in PE

- Intravascular volume increases in the postpartum period because of the mobilization of extracellular fluid to the intravascular space and "autotransfusion" of blood from the contracted uterus.
- The greatest risk of postpartum eclampsia is in the first 48 hours because of the profound shift of third space fluid to intravascular volume space after delivery, which may worsen hypertension [30].
- After delivery, it is common for patients to experience a short period of oliguria lasting up to 6 hours. To manage postpartum oliguria, it is recommended to restrict fluid intake after delivery and wait for natural diuresis, which typically occurs within 36–48 hours [5]. During this time, the combined of intravenous and oral fluids intake should be kept at 80 mL per hour or less. The intravenous fluids should be gradually reduced and eventually stopped when the patient can take and tolerate more than 80 mL of oral fluids per hour.
- This approach can help to prevent excess fluid overload.
- Replace appropriate blood products in postpartum hemorrhage, as in cases of placental abruption.

F. Oliguria in preeclampsia

- A short period (up to 6 hours) of oliguria in the immediate postpartum period is common and physiological, so wait and observe [11].
- Avoid administering fluids to treat this physiological oliguria (<15 mL/h urine output during the initial six hours in the postpartum period) [9].
- If oliguria persists after 6 hours, exclude pre-existing renal disease or a rising creatinine, and subsequently try the fluid challenge to rule out a pre-renal failure.
- A fluid bolus of 250–500 ml of normal saline or Ringer's lactate can be tried as a fluid challenge [13].
- Both dopamine and furosemide should be avoided to treat persistent oliguria [11].
- It is unlikely that short-term oliguria caused by severe preeclampsia will result in irreversible kidney damage.
- Postpartum persistent oliguria (beyond 24 hours) and increased plasma creatinine suggest postpartum renal failure [11].

FLUID MANAGEMENT IN POSTPARTUM HEMORRHAGE

Postpartum hemorrhage (PPH) is a major cause of maternal mortality and is estimated to cause around 30% of maternal deaths or 10 deaths every hour [31, 32]. The definition of PPH varies in different guidelines (Table 53.1). But the common definition of postpartum hemorrhage is blood loss of ≥500 ml for a vaginal delivery and ≥1000 ml for a cesarean birth [32, 33]. In addition, PPH is classified into two categories based on the severity of blood loss: minor (500–1000 mL) or major (more than 1000 mL). Major PPH is further divided into moderate PPH (1000–2000 mL) and severe PPH (more than 2000 mL) [34].

Uterine atony is the most common cause of primary postpartum hemorrhage, accounting for 80% of PPH. Other important causes of PPH are placenta previa, uterine rupture, trauma, placental abruption, and retained placenta.

Diagnosis and estimation of blood loss

It is challenging to estimate blood loss accurately in PPH. But all possible efforts should be made for its assessment because PPH can be a serious and potentially life-threatening condition.

The volume and speed at which blood is lost in PPH are often underestimated because the blood loss may be

Table 53.1 Postpartum hemorrhage definitions

Guidelines	Definitions
World Health Organization (WHO) 2012 [35]	Blood loss >500 mL within 24 hours
International Federation of Gynecology and Obstetrics (FIGO) 2012 [36]	Blood loss >500 ml in a vaginal birth and >1000 ml in a cesarean section
Royal College of Obstetricians and Gynaecologists (RCOG) 2016 [34]	Minor PPH: Blood loss 500–1000 ml without clinical shock Major PPH: Blood loss >1000 mL and continuous bleeding or clinical shock
Royal Australian and New Zealand College of Obstetricians and Gynaecologists, (RANZCOG) 2017 [37]	Blood loss >500 ml during the puerperium Severe PPH: Blood loss >1000 mL
American College of Obstetricians and Gynecologists (ACOG) 2017 [38]	Blood loss ≥1000 ml or more, or signs and symptoms of hypovolemia due to blood loss
NHS Obstetric Hemorrhage Clinical Guideline 2018 [39]	Primary minor PPH: Blood loss of 500–1000 ml within 24 hours of the birth of a baby Primary moderate PPH: Blood loss 1000–1500 mL within 24 hours Primary severe PPH: Blood loss ≥1500 mL within 24 hours Massive PPH: Blood loss ≥2000 mL within 24 hours, hemodynamic instability or sign of shock
A NATA consensus statement 2019 [40]	Primary PPH: Blood loss >500 mL within 24 hours Severe PPH: Blood loss >1000 mL within 24 hours with signs/symptoms of hypovolaemia Massive life-threatening PPH: Blood loss >2500 mL or hypovolemic shock

concealed. In addition, the physiological hemodynamic changes that occur during pregnancy may mask the typical clinical signs of hypovolemia. Hemodynamic changes which may occur after PPH is variable and depend on several factors such as hematocrit before delivery, cardiovascular status, and the rate of blood loss.

So, the correlation between blood loss and clinical signs is not reliable [41].

Clinical and laboratory parameters that can provide clues for early or undetected postpartum hemorrhage are summarized in Table 53.2.

Shock index: This is a simple-to-use parameter helpful to assess the amount of blood loss and the degree of hypovolemia in hemorrhagic shock, including PPH [43, 44]. The calculation of the shock index is simple: divide the heart rate by the systolic blood pressure. The normal value of the shock index is between 0.5 and 0.7, and a higher value indicates the presence of shock and is associated with hemodynamic instability.

The peak shock index may be a superior parameter for detecting PPH compared to heart rate or systolic blood pressure [45]. However, the shock index alone is not a good screening tool and should be used with other parameters [46].

Other methods: Various methods, such as visual estimation, direct measurement using calibrated drapes, and the gravimetric technique (which involves weighing blood-soaked materials), are used for estimating blood loss after vaginal birth. However, there is insufficient evidence to support the use of one method over another [47].

Due to the variable clinical signs of hemorrhagic shock and the lack of a rapid and reliable method to accurately detect the amount of blood lost early, the delay in diagnosis of postpartum hemorrhage and its severity is common. This can lead to a delay in therapy. Therefore, the initial step in the appropriate management of PPH is maintaining a high index of suspicion, and the onset of symptoms and signs of volume loss warrants aggressive volume replacement.

Fluid management in PPH

The medical strategy described as damage control resuscitation (DCR) is used to manage severe acute PPH. Its goal is to limit secondary blood loss, stabilize the patient's condition as quickly as possible and prevent further tissue damage [48, 49].

The main measures for damage control resuscitation include:

Table 53.2 Clues for early or undetected postpartum hemorrhage [42]

Clinical parameters	Laboratory parameters
Tachycardia (>100 bpm) in the absence of clinical hypovolemia and with adequate pain control	Hb fall >2 gm/dL before administration of IV fluids
Hypotension (BP ≤85/45 mmHg or blood pressure fall by 20% from the baseline value)	Severe metabolic acidosis (e.g., base excess <-4, pH <7.2)
Oliguria (urine volume <500 ml/day)	Shock index of >0.9
Persistent or recurrent maternal hypotension despite active fluid resuscitation and/or use of vasopressor drugs	High serum lactate level >4.0 mmol/L
Excessive requirement of IV fluids	Presence of coagulopathy
Cool extremities, tachypnea, inappropriate fear, restlessness, or confusion	-

1. Hypotensive fluid resuscitation.
2. Blood product transfusion.
3. To identify and control the sources of bleeding as quickly as possible by medical and damage control surgery.

Supportive measures such as raising the legs, administering oxygen, and warming the body in patients with PPH can help improve hemodynamic stability.

1. Fluid resuscitation

Draw blood for baseline measurements, and obtain an intravenous line with wide a bore cannula. Compared to 18 gauge, 14 gauge cannula can infuse almost double the fluid volume.

Until blood is available, start immediate rapid replacement with crystalloids or colloids for resuscitation and to maintain adequate tissue perfusion.

All crystalloids administered during resuscitation should be warmed and, if possible, given using rapid infusion devices to improve effectiveness and speed.

a. How much crystalloid to infuse?

For resuscitation in PPH, infuse crystalloids initially to maintain blood pressure while waiting for blood products. Two modalities with different approaches used for fluid resuscitation in PPH are the conventional aggressive approach and the currently recommended hypotensive fluid resuscitation approach [48].

b. Aggressive fluid resuscitation

The conventional aggressive approach is a traditionally used method in which large volume (>2 liters) of crystalloids are administered to rapidly expand the effective circulating blood volume and restore blood pressure and hemodynamic stability [50, 51]. But current recommendations advise against using an aggressive resuscitation strategy due to the potential for adverse effects, such as coagulopathy due to dilution of coagulation factors, third spacing of fluids, and hypothermia, which can occur due to infusion of large volumes of cold crystalloids [52], and resultant adverse maternal outcomes [53].

c. Hypotensive fluid resuscitation

Permissive hypotension, also known as hypotensive fluid resuscitation, is an alternative method currently recommended as the preferred strategy for treating PPH. This more cautious approach involves restricting the use of crystalloid fluids to maintain the patient's blood pressure lower than normal to limit secondary blood loss until control of bleeding is achieved and to prevent fluid overload [50, 54]. The aim of administering small crystalloid volumes is to provide adequate tissue perfusion and oxygen delivery to the body's tissues but reduce the risk of dilutional coagulopathy and prevent the disruption of pre-formed blood clots [48, 55]. Multiple studies have shown that hypotensive resuscitation can improve survival rates and is considered a safe and effective fluid resuscitation strategy [50, 56–58].

Recent guidelines recommend avoiding using more than 2 liters of crystalloid solutions or 1.5 liters of colloids in the treatment of PPH before resorting to blood transfusion [34, 59]. In treating PPH, it is more important to rapidly replace fluids and warm the solutions than to focus on the specific type of fluid being infused [34].

d. Goals of fluid therapy

Crystalloids should be followed immediately with packed red cell replacement using packed red blood cells (RBC) to restore oxygen-carrying capacity and maintain hemoglobin greater than 8 gm/dL.

The goal of therapy is to maintain systolic pressure of 80–90 mm of Hg, urine output >0.5 mL/kg/hr, and normal mental status. It is important to remember that, due to the benefits of permissive hypotension in PPH, the goal of therapy is not to maintain blood pressure in the normal range. So rather than following the standard practice of fluid administration, clinicians should adjust fluid infusion to maintain a target systolic blood pressure of 80–90 mm Hg until major bleeding has been controlled [60].

An alternative goal of fluid administration during the bleeding phase of severe postpartum hemorrhage is to achieve a low mean arterial pressure, which has been recommended to be between 50–60 mm Hg [60] and 55–65 mm Hg [40].

e. Colloids vs. crystalloids

Colloid solutions may be used as an alternative or an adjunct to crystalloids with the assumption of its greater and longer duration of volume expansion effect. But no colloid solution has been demonstrated to be superior to crystalloids. Compared to crystalloids, colloids are more expensive and carry a greater risk of adverse effects [61, 62]. According to guidelines from the World Health Organization (2012), an intravenous fluid replacement for PPH should be with isotonic crystalloids rather than colloids [35]. A Cochrane review (2018) that compared the use of colloids and crystalloids for fluid resuscitation in critically ill patients (excluding pregnant patients who had undergone cesarean section) found that resuscitation with colloids was not associated with an improvement in survival [20].

Based on these findings, for the resuscitation of women with PPH, isotonic crystalloids should be used in preference to colloids. Avoid dextrans in obstetric practice as they may interfere with platelet function and cross-matching and are hazardous [39]. Also, avoid using hydroxyethyl starch for resuscitation in major PPH [34].

f. Which crystalloid to give?

Ringer's lactate and normal saline are the two most commonly used crystalloid solutions for initial fluid resuscitation. They are routinely used, inexpensive, readily available solutions without significant side effects. Until blood is available, infuse crystalloid at a volume that is approximately three times the estimated volume of blood loss [39, 63].

Normal saline is usually administered in a labor ward because of its easy availability, low cost, and compatibility with blood transfusions and most drugs. But the infusion of large quantities (>2 L) of normal saline can cause hyperchloremic acidosis [63, 64] and acute kidney injury [65]. Ringer's lactate solution, compared to normal saline, has an electrolyte composition that more closely resembles plasma and can also buffer acidosis due to the metabolism of lactate to bicarbonate. Because of these properties, Ringer's lactate is considered more physiological than normal saline and is increasingly recommended as the first-choice resuscitation fluid [66].

Dextrose-containing IV solutions, such as 5% dextrose or dextrose with saline, should not be used in treating PPH because the rapid infusion of these solutions can cause hyperglycemia and resultant diuresis.

2. Blood replacement

Timely and adequate blood replacement is crucial and lifesaving in the treatment of severe PPH.

a. Intravenous fluids vs. blood

Because of the potential harms of large-volume crystalloid resuscitation (e.g., dilution coagulopathy, volume overload, and hypothermia) [67, 68], early blood transfusion should be managed after initial fluid administration.

The trend is growing (hemostatic resuscitation) to transfuse blood components early to correct hypovolemia and allow permissive hypotension in severe acute PPH [40, 48, 55, 69]. The rationale of this strategy is to reduce the contribution of crystalloid solutions and thereby prevent side effects associated with the administration of a large volume of crystalloids.

b. Indications of blood replacement

There are no clear guidelines for determining when a red blood cell transfusion should be infused [70, 71]. Patients with acute hemorrhage can have normal hemoglobin, so it is important to pay close attention to the clinical evaluation [71].

Common indications of red cell transfusion in PPH are [34, 38, 71–75]:

- Women with a hemoglobin value <6 gm/dL, irrespective of symptoms.
- Clinically severe uncontrollable postpartum hemorrhage.
- Blood loss of 1500 ml or more usually requires blood/pack cell transfusion.
- Blood is usually administered to symptomatic women (maternal tachycardia >110 beats per minute, dizziness, syncope) with active bleeding, irrespective of hemoglobin status. Do not wait for laboratory results; the decision to provide a blood transfusion should be based on clinical signs to avoid delay.
- The combination of a higher shock index (>9) and lactate levels (>4.0 mmol/L), with immediate postpartum lower hemoglobin, predicts the requirement for blood transfusion.
- Blood transfusion is usually not required when blood loss due to PPH is small, and the woman is asymptomatic.
- Women with PPH rarely require a blood transfusion if the hemoglobin is more than 10.0 gm/dL.

c. Selection of blood product

Packed red blood cells (PRBCs) are preferred for resuscitation and to avoid crystalloids-induced dilutional coagulopathy in women with massive hemorrhage. In cases of life-threatening PPH when the patient's blood group is unavailable or there is an anticipated delay in receiving cross-matched blood, consider using O Rh negative blood [34, 76].

Packed red blood cells are the preferred treatment for hypovolemic shock caused by hemorrhage, and each unit can be expected to increase the hemoglobin level by about 1 gm/dL [77].

Transfusion ratios: When a large volume of transfusion is required, recommended proportionate administration of red blood cells, fresh frozen plasma (FFP), and platelets are in a 1:1:1 ratio, which resembles the replacement of whole blood [38, 78]. Blood products transfused in a ratio, mimicking whole blood replacement, are associated with lesser complications and better survival [79].

d. Post-transfusion goals

The post-transfusion goals in the management of PPH are to maintain the following [80]:

- Hemoglobin level greater than 8 gm/dL.
- Platelet counts greater than 50,000/mm3.
- Fibrinogen level greater than 150–200 mg/dL.
- Prothrombin time is less than 1.5 times the normal value.

e. Adverse effects

With the changing trend to use early transfusions to achieve faster hemodynamic stability and avoid using the large volume of crystalloids, a higher incidence of transfusion-related complications due to the administration of multiple units has been observed. Complications frequently encountered are hyperkalemia, hypocalcemia, allergic reactions, citrate toxicity, volume overload, and transfusion-related acute lung injury (TRALI).

Hyperkalemia and hypocalcemia (low ionized calcium) are common electrolyte abnormalities seen whenever multiple units of stored PRBCs are transfused rapidly. The risk of hyperkalemia is high following a massive transfusion because older stored PRBCs contain about 5 mEq of potassium per unit (300 mL).

The risk of developing hypocalcemia is high after rapidly transfusing large amounts of blood due to the presence of citrate, an anticoagulant, in the blood. Each unit of packed red blood cells contains about 3 mg of citrate. In very sick patients, the liver's ability to eliminate citrate may be impaired, leading to citrate accumulation in the blood. Accumulated citrate binds to circulating ionized calcium, leading to hypocalcemia and can cause citrate toxicity. Therefore, monitoring for and managing citrate toxicity in patients receiving large amounts of PRBCs or who have compromised liver function is essential Patients receiving large amounts of blood need the administration of calcium injections to prevent or correct hypocalcemia.

Ringer's lactate and blood should not be administered in the same line because the calcium in the RL solution may cause clotting.

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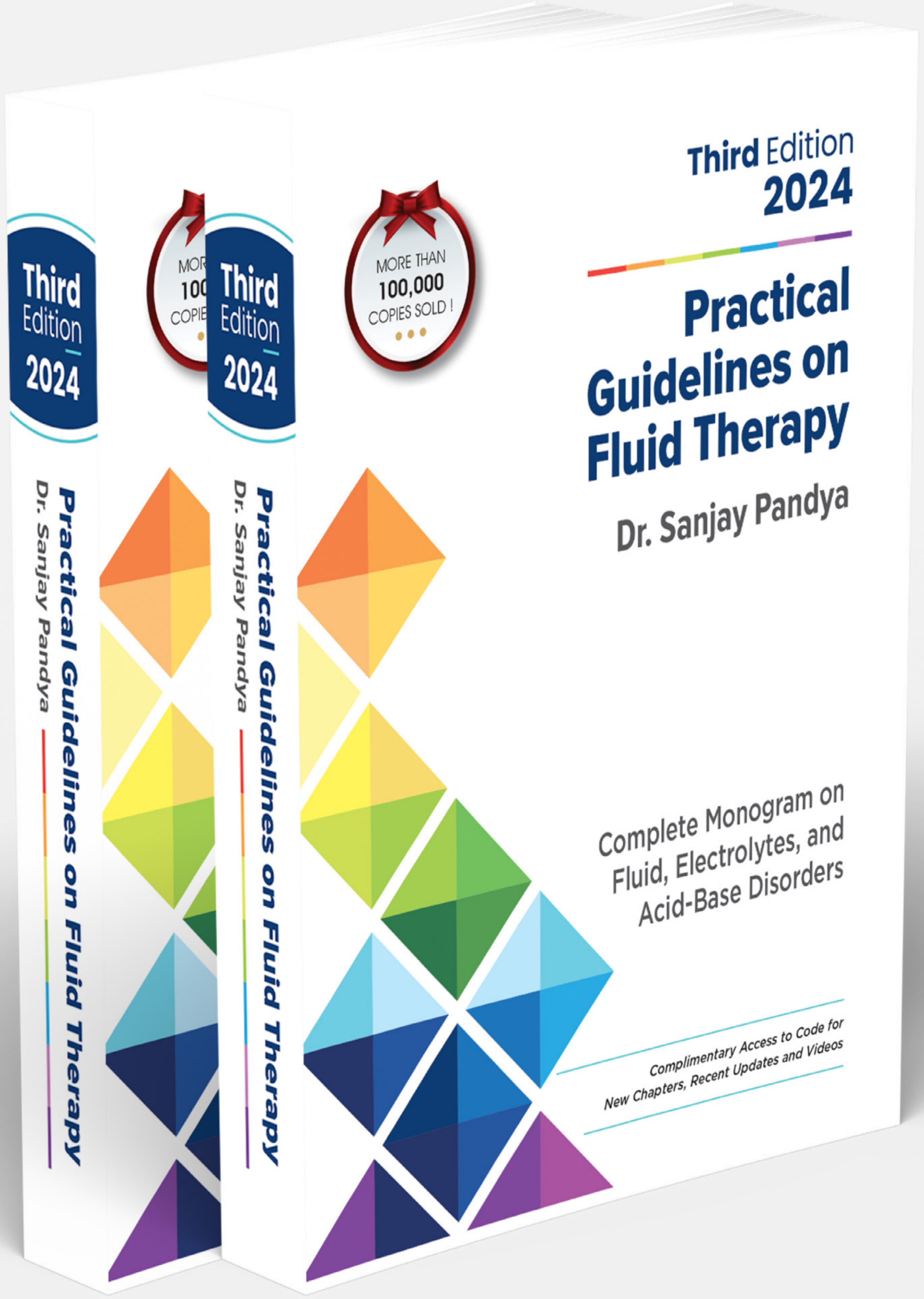
Chapter 54:

Hyponatremia during Labor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Hyponatremia during Labor

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Labor per se does not cause hyponatremia (defined as serum sodium <130 mEq/L), but during labor, women are at increased risk of developing the same [1]. Hyponatremia following prolonged labor is not uncommon and is potentially hazardous to the mother and neonate [2, 3].

PHYSIOLOGICAL PREDISPOSING FACTORS

Women in labor are at greater risk of developing hyponatremia than non-pregnant women [4] because of:

1. Lower baseline plasma sodium. The normal range of serum sodium concentration is lower (130–140 mEq/L) in pregnancy compared to its value in non-pregnant adults (135–145 mEq/L) [4, 5]. In the late third trimester, about 6 to 8 liter of water is retained, which is responsible for the dilutional hyponatremia and the lower baseline plasma sodium value.
2. An impaired renal ability to excrete water [6, 7]. In healthy women, the normal capacity of kidneys to excrete a water load is 900 ml/h. While in late pregnancy, the maximum renal ability to excrete a water load reduces to 600 mL/h [8]. In the presence of the tendency of kidneys to retain water, hyponatremia is likely to occur if the excess fluid is consumed orally or administered intravenously.
3. Antidiuretic effect of endogenous oxytocin. As the structure of oxytocin is similar to vasopressin, oxytocin causes water retention and results in dilutional hyponatremia in laboring women [9]. Reasons for the higher concentration of oxytocin during labor are the greater release of endogenous secretion of oxytocin and IV administration of synthetic oxytocin to induce or augment labor.

CAUSES

Causes of maternal hyponatremia are:

1. Excessive oral water intake during prolonged labor [10, 11].
2. Hyponatremia is likely in women who choose home delivery but are transferred to the hospital after prolonged labor due to unsuccessful delivery or obstetric complications [3]. The mechanism for developing hyponatremia in such patients is the high endogenous secretion of oxytocin and excessive oral hypotonic fluid intake.

3. Liberal fluid administration causes iatrogenic maternal fluid overload.
4. Increased oral fluid intake and intravenous fluid administration are major causes of hyponatremia. Hyponatremia occurs when the intake of low sodium-containing fluid exceeds a woman's ability to excrete it during labor. Water retention causes a decrease in the concentration of sodium by diluting the blood. As a result, the incidence of hyponatremia at delivery among women is 1% for those with a total fluid intake (oral + IV) of up to 1 liter during labor and 5% for those with a total fluid intake between 1 to 2.5 liters [2]. The risk of hyponatremia increases to as high as 26% for those with a total fluid intake above 2.5 liters.
5. Administration of a large volume of oxytocin in hypotonic solutions (i.e., 5% dextrose) for a prolonged period for induction and augmentation of labor can cause hyponatremia [2].
6. Other causes: Hyperemesis gravidarum, psychiatric disorders, and maternal medications like diuretics, antidepressants like selective serotonin reuptake inhibitors [SSRIs], and synthetic recreational drugs like ecstasy.

HARMFUL EFFECTS

Hyponatremia during labor can produce deleterious consequences for both the mother and the neonate. In addition to the usual symptoms of hyponatremia (e.g., nausea, lethargy, headache, agitation, confusion, drowsiness, seizures, etc.), maternal hyponatremia is associated with the prolongation of the second stage of labor, instrumental birth, and emergency cesarean birth for failure to progress [2].

As water diffuses freely across the placenta, maternal hyponatremia can lead to neonatal hyponatremia [12, 13]. Significant hyponatremia in newborns may cause irritability, lethargy, and feeding difficulties in mild cases and seizures, respiratory distress, apnea, hyperbilirubinemia, and coma in severe cases [10, 14–16].

PREVENTION

Measures which help to prevent hyponatremia are [1]:

1. Strict fluid balance chart and early recognition: Record oral/intravenous fluid intake and urine output every four hours for close monitoring. When an electrolyte imbalance is suspected, it is important to measure the serum electrolytes. If a woman's fluid balance exceeds positive 1500 ml, her risk of developing hyponatremia is high, and her blood sodium level should be checked.
2. Neutral fluid balance: Maternal dilutional hyponatremia can be prevented during labor by maintaining a neutral fluid balance. Therefore, excessive fluid intake during labor should not be encouraged for women.
3. Avoid the administration of hypotonic IV fluids like 5% dextrose during labor.
4. When oxytocin is to be administered in a high dose for a prolonged period, use a higher concentration of oxytocin to reduce the total volume of infused fluid, use electrolyte-containing solutions such as normal saline or Ringer's lactate as a diluent, and avoid electrolyte free solution like 5% dextrose as a diluent.
5. During labor, it is important to monitor serum sodium levels in women who require oxytocin infusion, have a positive fluid balance exceeding 1500 ml, develop symptoms of hyponatremia,

or have a serum sodium level less than 130 mEq/L.

TREATMENT

Treatment depends on the underlying cause. The basic principle of treating dilutional maternal hyponatremia is a fluid restriction (oral and intravenous), discontinuation of oxytocin infusion, and co-administration of furosemide if there is any evidence of fluid overload [1]. Administration of hypertonic saline is necessary for patients with severe clinical symptoms due to hyponatremia (such as seizures or loss of consciousness) with close monitoring of sodium levels.

Hypovolemic depletion hyponatremia is less common during labor and may need IV fluid administration. Normal saline is a preferred solution in such women. For detailed information about the treatment of hyponatremia, please refer to Chapter 20 on "Hyponatremia".

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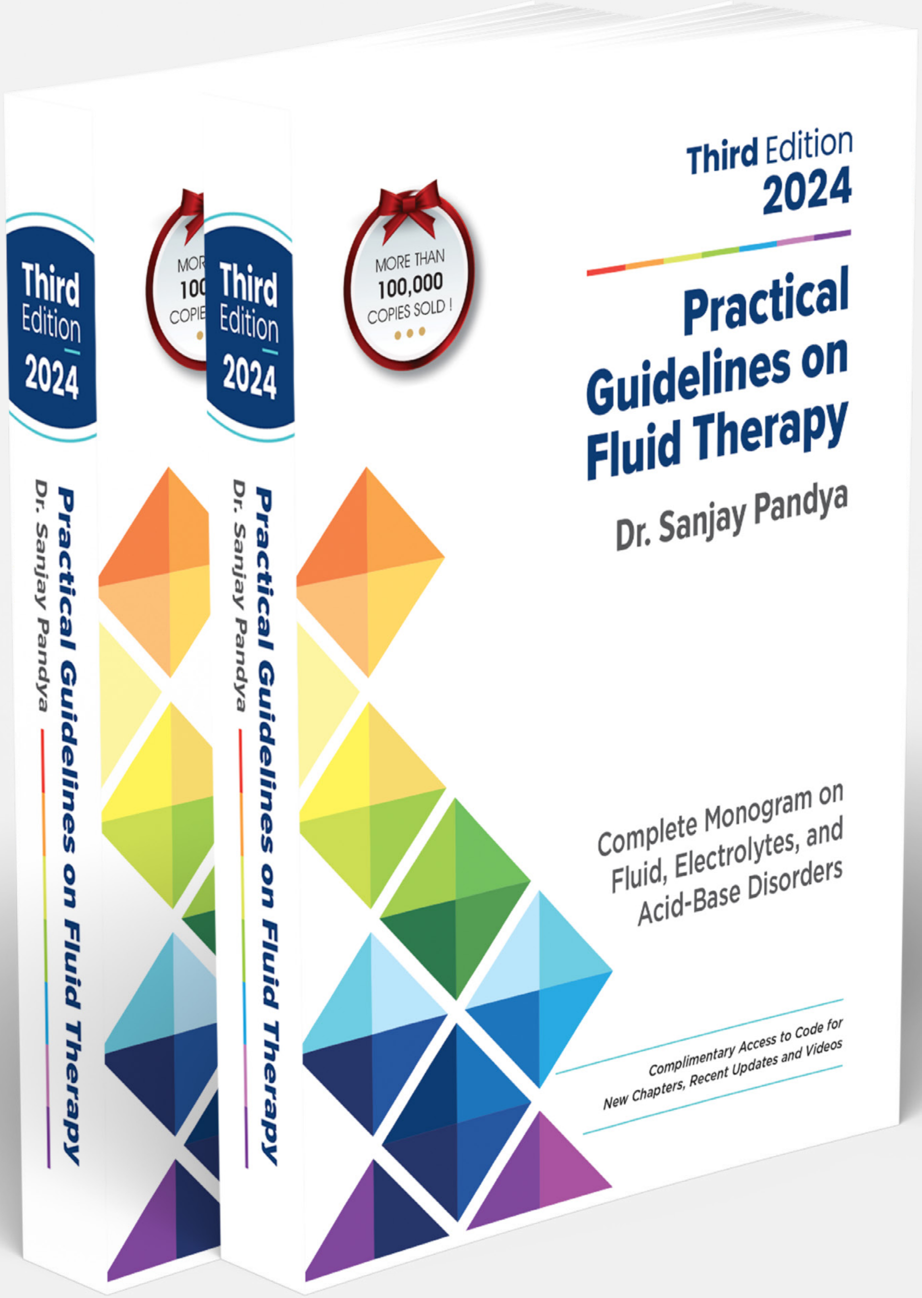
Chapter 55:

Parenteral Nutrition: Principles and Requirements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Parenteral Nutrition: Principles and Requirements

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Parenteral nutrition (PN) is currently one of the most sophisticated forms of intravenous therapy. Appropriate use of parenteral nutrition is lifesaving when there is no other option for nutrition.

DEFINITION

Parenteral nutrition is a method of intravenous administration of nutrients, vitamins, electrolytes, and medications to patients who cannot take or tolerate enteral nutrition or have a non-functional gastrointestinal tract.

PN is an effective means of sustaining life and promoting recovery in critically ill patients incapable of ingesting, absorbing, or assimilating nutrients. Similarly, PN is a life-supporting therapy even for non-critically ill patients with pre-existing malnutrition and for non-stressed but hospitalized patients who cannot take oral intake for 5 to 7 or more days.

BASIC PRINCIPLES OF NUTRITION

- Avoid malnutrition as it is harmful [1].
- If the intestines are functioning properly, utilize them. When possible, it is recommended to use enteral nutrition instead of parenteral nutrition. However, ensuring the safe and sufficient delivery of nutrition is of higher priority than the route of delivery.
- Avoid overfeeding, as it can cause significant complications. Excess carbohydrates can cause hyperglycemia, hepatic steatosis, and increased CO_2 production; excess protein can cause azotemia and metabolic acidosis, and excess fat can cause hyperlipidemia [2, 3].
- While planning PN, more critical factors are the method of delivery, timing, and the type of formula rather than the specific amounts of nutrients provided.
- During acute stress, the body mobilizes endogenous amino acids and energy stores. It is not possible to make catabolic patients anabolic entirely. The goal of nutritional support is to prevent the wasting of protein and to provide essential and conditionally essential nutrients.

Importance of avoiding malnutrition

Malnutrition should be prevented due to its harmful consequences, including:

- Malnutrition leads to increased morbidity and mortality and should be avoided. In addition, it leads to increased susceptibility to infection, poor wound healing, pulmonary complications (weakness of respiratory muscles leading to the decreased ventilatory drive, reduction of vital capacity, and depressed lung defense due to reduces cough pressure and removal of secretions), electrolyte disturbances, and postoperative complications.
- Malnutrition leads to a prolonged recovery period and a longer duration of hospitalization.
- It can negatively impact the quality of life and is associated with higher morbidity and mortality.

Goals of parenteral nutrition

The role of PN is supportive. The principal goals of nutritional support are:

- To sustain or improve nutrition by administering all necessary nutrients such as proteins, carbohydrates, lipids, electrolytes, minerals, trace elements, and vitamins.
- To decrease the negative impacts of catabolism, it is essential to maximize protein synthesis, limit the breakdown of body protein, and slow down the rate of weight loss.
- To boost the immune function and to improve wound healing.
- Restoring glycogen storage increases the strength of cardiac and diaphragmatic muscles and improves cardiopulmonary function.
- To maintain or correct acid-base and electrolyte disturbances.

Table 55.1 Planning of parenteral nutritional support

1. Selection of patient: Determine if PN is truly indicated. PN is recommended only when potential benefits (improvement in prognosis and quality of life) exceed the risks.
2. Select and establish an appropriate route of administration on the basis of long-term vs. short-term requirements.
3. Calculations of nutritional requirements: Calculate the requirements of fluid, energy, glucose, lipids, proteins, minerals, and vitamins for individual patients (along with disease-specific modifications).
4. Prescribe parenteral nutrition: Convert nutritional requirements to prescription. Prepare or select an optimal formula to deliver nutrients.
5. Administration, monitoring, and avoiding complications of PN support.

- To accelerate recovery and improve the quality of life.

Planning parenteral nutrition

Planning of parenteral nutritional therapy is summarized in Table 55.1.

ENTERAL NUTRITION VS. PARENTERAL NUTRITION

Preference of EN over PN

Enteral nutrition (EN) is preferred when the gastrointestinal tract is functional and accessible. The potential benefits of enteral feeding are:

- Maintains mucosal integrity: Provides nutrients that are needed in the intestinal lumen to maintain the structural and functional integrity of the gastrointestinal (GI) tract. Enteral feeding prevents the atrophy of intestinal mucosa and maintains mucosal functions of the gut. Intact mucus membrane preserves the barrier functions of the bowel and prevents bacterial translocation, and therefore prevents the possible risk of sepsis.
- Unlike standard PN, EN provides gut-preferred fuels such as glutamate and short-chain fatty acids.
- More physiological as the liver is not bypassed. The complete volume of nutrient-rich venous blood from all parts of the gastrointestinal tract passes from the liver before it returns to the heart. So hepatic take-up, process, and storing of various nutrients from the venous blood and subsequent release on neural or hormonal command is maintained with EN.
- Prevents cholelithiasis by stimulating gall bladder motility.
- Fewer serious complications and avoids known and potential complications of PN.
- Less costly and easier to maintain than PN. Because of the potential advantages of EN, the provision of even “token” enteral supplementation is recommended to patients receiving total PN support whenever possible.

Contraindications EN

Major contraindications of enteral nutrition are:

- Gastrointestinal causes: Active severe gastrointestinal bleeding, small or large bowel obstruction, perforation, generalized peritonitis, severe paralytic ileus, high output external fistula, and intractable vomiting or diarrhea refractory to medical management.
- Cardiac causes: Active shock or

severe hemodynamic instability with poor end-organ perfusion and hypotensive patients on a high dose of inotropes/vasopressors. Avoid EN in patients who are hemodynamically unstable and not fully resuscitated [4, 5], but due to multiple benefits of EN [6, 7], initiate EN after adequately fluid resuscitation once the patient is stable and/or doses of vasopressors are declining [8, 9].

- Lack of access: Unobtainable safe access to the gastrointestinal tract.
- Complications of enteral feeding: Patients with enteral feeding complications (i.e., pulmonary aspiration, severe diarrhea, and intestinal ischemia or infarct precipitated by enteral feeding in patients with ischemic bowel syndrome) should not be fed by the enteral route.

Advantages of PN over EN

Potential advantages of parenteral nutrition over enteral nutrition are:

- Ensured desired volume delivery of nutrients without the concerns of gastrointestinal intolerance or compliance with transnasal feeding tubes.
- Improved metabolic, electrolyte, and micronutrient management.
- Better acid-base manipulation.
- Drug delivery capabilities (histamine H2 blockers, metoclopramide, insulin, heparin, etc.).

So, PN not only delivers nutrition but also regulates fluid, electrolyte, and acid-base homeostasis.

Factors considered while selecting parenteral nutritional support

The decision to use parenteral nutrition should take into account several important factors, including:

- Age and premorbid state (healthy or otherwise).
- Nutritional status, including endogenous fuel (fat) and protein (muscle) stores, weight loss, and serum albumin value.
- Duration of starvation and degree of the anticipated insult.
- Underlying disease, its severity, and concomitant medical therapy.
- Gastrointestinal function and the possibility of resuming normal intake soon.

INDICATIONS OF PARENTERAL NUTRITION

Parenteral nutrition is required in patients who cannot, should not, or will not eat enough to maintain adequate nutrition and are at risk of developing malnutrition. PN prevents the adverse effects of malnutrition and prevents or corrects specific nutrient deficiencies when the gastrointestinal tract cannot be used efficiently or safely for a prolonged period. Additionally, using PN can reduce total hospitalization costs due to faster recovery and reduced complications of the underlying condition.

However, PN is expensive and has the potential for serious complications. So benefits of PN should be weighed against the potential risks before initiating PN. Important indications of PN are summarized in Table 55.2 [10–12].

ADVANTAGES AND DISADVANTAGES OF PN

Major advantages and disadvantages of the parenteral nutrition are as follows:

Major advantages

- Lifesaving when the GI tract cannot be used.
- Ensured desired volume delivery of nutrients when:

Table 55.2 Indications of parenteral nutrition

A. General indications
1. Critical illness with inadequate oral or enteral nutrition for >5–7 days
2. In critically ill patients with severe malnutrition or high nutrition risk, initiate PN as soon as feasible if oral or enteral nutrition is not possible or inadequate

B. Anticipated or actual inadequate oral or enteral intake
1. Conditions that impair the absorption of nutrients
    a. GI fistula
    b. Short bowel syndrome
    c. Small bowel obstruction
    d. Effects of radiation or chemotherapy
2. Need for bowel rest
    a. Severe acute necrotizing pancreatitis
    b. Inflammatory bowel disease
    c. Mesenteric ischemia
    d. Peritonitis
    e. Perioperative (bowel resection, major gastrointestinal surgery)
3. Motility disorders
    a. Prolonged ileus
4. Inability to achieve or maintain enteral access
    a. Haemodynamic instability
    b. Massive gastrointestinal bleeding
    c. Unacceptable aspiration risk
    d. Hyperemesis gravidarum, eating disorders

C. Significant multiorgan system disease
- Significant renal, hepatic, and pulmonary diseases or critical illness (multi organ failure, severe head injury, burns, etc.), which prevents adequate oral or EN

    - GI intolerance prevents oral or EN.
    - Less than 2 to 3 feet of the small intestine.
- Easier correction of fluid and electrolyte disturbances.

Major disadvantages
- High cost.
- Catheter-associated infections and complications.
- Fluid overload and electrolyte abnormalities.
- More risk of metabolic problems like hyperglycemia, hypercholesterolemia, hepatic dysfunction, and refeeding syndrome.
- Leads to intestinal mucosal atrophy, causing damage to the gut barrier. Loss of this first line of defense predisposes patients on PN to risk bacteremia and infection.
- Daily PN is cumbersome.

CONTRAINDICATIONS OF PN

Contraindications of PN are broadly discussed in two groups:

General contraindications

- If enteral or oral nutrition meets the patient's nutritional requirements.
- Patients are well-nourished, stable,

non-catabolic, and within the short term (five to seven days), oral or enteral nutrition is likely to be initiated. For Most patients who require short-term support, the risks of PN outweigh the benefits.

- Severe liver failure, cardiac failure, cardiogenic shock, and blood dyscrasias.
- Cautious use in hemodynamic instability, volume overload, azotemia (BUN >100 mg/dL), severe hyperglycemia (glucose >300 mg/dL), or electrolyte disturbances (Na^+ >150 mEq/L, K^+ <3 mEq/L, Cl^- <85 mEq/L and phosphorus <2 mg/dL), where administration of PN carries high risk.
- Undue high risk in the insertion of catheter solely for PN.
- To prolong life in terminally ill patients with a poor expected outcome when there is little prospect of good quality of life.

Disease-specific contraindications

- Excess use of carbohydrates results in the production of a large amount of carbon dioxide and therefore should be avoided in patients with compromised pulmonary function and with ventilator support during the weaning period.
- Use lipid administration with caution if the triglyceride level is consistently more than 350 mg/dL or in patients with severe sepsis, a moderate degree of jaundice, low platelet count (<50,000 to 60,000/mm), and ARDS or severe respiratory disease.
- Avoid the use of excess PN volume in patients with heart or kidney failure.
- In patients with hepatic encephalopathy and severe renal failure, modified amino acids are preferred over standard amino acids.

It is important to remember that parenteral nutrition must not be undertaken lightly. It is potentially harmful and dangerous if not administered with due precautions.

Timing of parenteral nutrition initiation

Even in critical patients, the decision to start PN is never an emergency. Before starting PN, if the patient is hemodynamically stable and there are no electrolyte or blood glucose abnormalities, the risks of adverse effects of PN are low. At times adequate initial therapy of critical illness may sufficiently improve clinical status to permit oral or EN, and the patient may not require PN. Early PN benefits severely malnourished, critically ill patients, patients with severe necrotizing acute pancreatitis, and high output fistula with large nutrient losses.

NUTRITIONAL REQUIREMENTS

Basic nutritional requirements include a balanced amount of fluid, macronutrients (carbohydrates, lipids, proteins), and micronutrients (electrolytes, minerals, trace elements, and vitamins).

A. Fluid requirements

The total fluid requirement in an adult patient can be calculated by adding abnormal losses to normal daily fluid requirements. In adult patients of average-sized, the fluid requirements are about 25–30 mL/kg/d. Correct volume deficit before initiating PN. Search and replace fluid additionally to replace abnormal fluid losses caused by diuretic therapy, diarrhea, vomiting, nasogastric tube drainage, wound output, perspiration, etc. Patients with fluid overload due to cardiac, pulmonary, hepatic, or renal failure need fluid restriction. The volume of fluid delivered by the enteral route should be subtracted from the estimated total fluid requirement. Significant minerals are lost with enteric fluid loss, so an extra amount of these nutrients and fluid must be added to the parenteral solution.

B. Energy requirements

PN should provide adequate energy to patients. Four components of daily energy requirements/total energy expenditure (TEE) are resting energy expenditure-REE (normally two-thirds of TEE), activity energy expenditure (activity factor-AF, normally one-fourth to one-third of TEE), the thermal effect of food (Thermal factor-TF, normally 10% of TEE) and associated illness (disease factor-DF). Adult patients' appropriate total energy requirement is 20–30 kcal/kg/d [13].

Total energy expenditure can be estimated by any of three methods (Table 55.3):

- By using a simple calculation based on calories per kilogram of body weight.
- By using Harris-Benedict (HB) equation to calculate resting energy expenditure, plus additional calories for activity and illness or,
- By calculating energy expenditure with indirect calorimetry.

1. Simple body weight-based calculation

Energy requirements can be calculated roughly by multiplying actual body weight in kilogram by 25–30 kcal, which needs modifications considering physical activity and associated illness (Table 55.4). In obese patients, use ideal body weight

Table 55.3 Methods for estimating total energy expenditure (kcal)

1. Simple body weight based calculation: • REE (kcal/day) = 30 × weight in kg
2. Harris-Benedict equation: • REE (Man) = 66 + (13.7 × W) + (5.0 × H) - (6.7 × A) • REE (Women) = 655 + (9.6 × W) + (1.8 × H) - (4.7 × A)
3. Indirect calorimetry: • REE (Man) = (3.9 × VO2) + (1.1 × VCO2) - 61
A: Age in years; H: Height in cm; W: Weight in kg; REE: Resting energy expenditure

Table 55.4 Guidelines for adjustment in energy requirements

AF = Activity factor	DF = Disease factor	TF = Thermal factor
1.2 bed rest	1.10 on ventilator	1.1 38°C
1.3 out of bed	1.25 general surgery	1.2 39°C
1.4 active	1.3 sepsis	1.3 40°C
-	1.6 multiorgan failure	1.4 41°C
-	1.7 30–50% burns	-
-	1.8 50–70% burns	-
-	2.0 70–90% burns	-

for calculation. Severely malnourished critically ill patients are at high risk for refeeding syndrome, and therefore while initiating PN, administer hypocaloric PN (energy intake less than 20 kcal/kg/d) with adequate protein intake.

2. **Harris-Benedict equation**

   While calculating REE by the Harris-Benedict equation, undernourished patients use actual body weight, and obese persons use ideal body weight.

   To calculate TEE from REE, it is necessary to correct for physical activity (activity factor-AF), associated illness (disease factor-DF), and temperature (TF) as per Table 55.4.

   So, TEE = REE × AF × DF × TF

3. **Indirect calorimetry**

   Above both methods fails to provide accurate calculations of the actual energy used, especially for patients who are significantly underweight, overweight, or critically ill. Therefore, indirect calorimetry using the multi-component metabolic carts [14] is considered the gold standard method to evaluate energy expenditure in clinical practice. As this accurate and non-invasive technique helps in planning the prescription of nutrition and prevents both under and overfeeding in patients by spontaneously breathing and ventilation, its routine use to optimize nutrition care should be encouraged [15, 16].

   Calculation based on body weight and the HB equation is simple but often overestimates energy expenditure. Because of the complications of overfeeding, it is wiser to administer lesser calories rather than too many calories.

Providing energy requirements in parenteral nutrition

The approximate proportion of various macronutrients, including carbohydrates, lipids, and proteins, in the parenteral solution for energy supplementation is summarized in Table 55.5. Generally, the energy content of parenteral nutrition predominantly consists of carbohydrates and lipids (non-protein calories), as proteins are primarily directed towards anabolic processes rather than serving as an energy source. In clinical practice, a common approach is to provide approximately 60–70% of calories from glucose and 30–40% from lipids. This combination of fuel sources in critically ill patients significantly reduces carbon dioxide (CO_2) production, improving patient outcomes

In clinical practice, glucose and lipids are usually given roughly 60–70% glucose and 30–40% lipids.

This mixed fuel nutrient in stressed patients significantly reduces CO_2 production and, therefore, reduces the respiratory work of breathing.

Avoidance of overfeeding in parenteral nutrition

Overfeeding is associated with several significant complications that must be carefully managed to optimize patient outcomes. These complications include:

Table 55.5. Macronutrient composition in parenteral nutrition solutions

Macronutrient	% Contribution	Calories per gm
Carbohydrates	50–60%	1 gm dextrose = 3.4 kcal
Lipids	20–30%	1 gm lipid = 9 kcal
Proteins	15–20%	1 gm protein = 4 kcal

- Severe hyperglycemia: Overfeeding can lead to severe hyperglycemia, resulting in glycosuria, osmotic diuresis, and dehydration.
- Increased risk of infections: Hyperglycemia caused by overfeeding can elevate the risk of nosocomial infections.
- Increased oxygen consumption: Excessive calorie administration can lead to increased oxygen consumption and carbon dioxide production. This heightened metabolic rate may necessitate increased respiratory effort, potentially causing problems in patients with compromised lung function.
- Hepatic steatosis: Overfeeding and excess calorie intake can contribute to the accumulation of fat in the liver, leading to hepatic steatosis. This condition can result in long-term hepatic dysfunction [17].

C. Carbohydrates

Dextrose is the least expensive and most commonly used - a primary source of calories in parenteral nutrition.

1. Caloric value, preparations, and requirements

Each gm of hydrated dextrose monohydrate used to prepare parenteral nutrition supplies 3.4 kcal (The caloric contribution of dietary carbohydrate is 4 kcal/gm). Commercially made formulas are available in a concentration ranging from 5% to 70% (Table 55.6). Most central parenteral nutrition (CPN) formulations use dextrose in concentrations ranging from 50–70%, which is then diluted to 15–30% when mixed with other macronutrients. Usually, 50–70% of the total energy requirement is provided in the form of dextrose. Dextrose requirements are about 4–5 mg/kg/min in stable patients and less than 4 mg/kg/min in critically ill, trauma, and sepsis patients and should not exceed 5 mg/kg/min [13, 18]. The minimal requirement of carbohydrates for PN is about 2 gm/kg/d of glucose [19].

Start with no more than 150 to 200 gm of dextrose on the first day of PN. In patients with diabetes or patients at risk for refeeding syndrome, start with a lower dose (100 to 150 gm) of dextrose.

2. Functions and advantages

- Low cost: Dextrose is the least expensive macronutrient and hence, most commonly used.
- Supplies calories: Parenteral carbohydrate in the form of dextrose in PN is the primary source of calories. Many tissues, such as erythrocytes, white blood cells, and renal medulla, rely primarily on glucose as an energy source and cannot easily use alternative fuels. Brain tissues, red blood cells, immune cells, and renal medulla preferentially use glucose as fuel [19]. So, it is safer to provide a minimum of 100–150 gm (about 2 gm/kg body weight) of dextrose per day to meet these demands [18].

Table 55.6 Characteristics of dextrose solutions

Solution concentration	5%	10%	20%	25%	50%	70%
Dextrose content (gm/L)	50	100	200	250	500	700
Supply of calories (kcal/L)	170	340	680	850	1,700	2,380
Osmolarity (mOsm/L)	253	505	1,010	1,330	2,525	3,535

- Nitrogen-sparing effect: Adequate carbohydrate supplementation has an important nitrogen-sparing effect, especially in patients with metabolic stress. When calories are provided as glucose, it stimulates insulin secretion, reduces muscle protein breakdown, and reduces the release of glucose from the liver. Thus, dextrose prevents protein catabolism by inhibiting the release of amino acid precursors from skeletal muscle for gluconeogenesis. In addition, glucose oxidation is also stimulated, thus sparing the oxidation of amino acids.

3. Disadvantages

- Low-calorie supply: Dextrose is a poor source of calories (3.4 kcal/gm of dextrose vs. 9.0 kcal/gm of fat). So to meet the total calorie requirements, the patient either needs a larger fluid volume (if we use diluted dextrose solution) or a highly concentrated dextrose solution (which can cause thrombophlebitis).
- Hyperglycemia: The development of hyperglycemia is the most common drawback of dextrose in PN. The risk and severity of hyperglycemia are greater with IV dextrose than with the same amount of oral or enteral administration because IV dextrose bypasses the entero-insular axis. Hyperglycemia due to a larger amount of dextrose limits the increment in the dose of dextrose in PN.
- Increased CO_2 production (high respiratory quotient): Carbohydrates produce more carbon dioxide compared to lipids, which increases the work of respiratory muscles to eliminate carbon dioxide. Therefore, carbohydrate is not preferred as an only source of calorie in respiratory compromised patients and patients weaning from ventilator support.
- Thrombophlebitis: Concentrated dextrose solution (above 10%) has high osmolarity as compared to plasma osmolarity (280 mOsm/L), so it can cause thrombophlebitis, requiring a central line for administration.

4. Administration of dextrose infusion and monitoring

The infusion rate of dextrose should not exceed the body's glucose oxidative capacity. The maximum rate of dextrose oxidation is approximately 4–5 mg/kg/min (5.8–7.2 gm/kg/day). Providing an excess amount of dextrose increases the risk of complications such as hyperglycemia, fatty liver, respiratory problems due to excess CO_2 production, and increased infectious-related mortality. Therefore, in patients at high risk of developing hyperglycemia (pre-existing diabetes, sepsis, obesity, steroid therapy, etc.), initiate carbohydrate infusion at a low rate (i.e., 1–2 gm/kg body weight/day). Monitor dextrose infusion closely and maintain blood sugar levels between 140–180 mg/dL [20]. Administer regular insulin only if necessary. Insulin therapy is usually initiated in diabetic patients when blood sugar is more than 140 mg/dL and in non-diabetic patients when blood sugar is more than 180 mg/dL [21].

To control hyperglycemia, insulin can be administered using different regimens, but the continuous infusion of insulin and adding insulin to the nutrition bag are common and efficient methods [21–23].

5. Example of calculation of carbohydrate/dextrose requirements

Example: For a 60 kg male with 25 kcal/kg/d energy requirements, how much 50% dextrose solution is needed (considering 60% of daily total energy requirement in the form of carbohydrates) in a day?

Calculation:

- Total caloric requirements will be 60×25=1500 kcal/day, and carbohydrate requirement will be 900 (60% of 1500) kcal/day as dextrose.
- Divide caloric requirements from carbohydrates by 3.4 (there is 3.4 kcal/gm of dextrose) to determine the gm of dextrose required. 900 divided by 3.4 = 264.7 gm of dextrose/day.
- D50% has 50 gm of dextrose per 100 ml. So to provide 264.7 gm of dextrose/day required volume of D50 will be about 529 ml/day (22 ml per hour).

D. Protein

Protein supplementation is an essential component of parenteral nutrition. The primary source of protein supplementation in parenteral nutrition is free amino acids. Amino acids given in PN are not provided as an energy substrate. But the rationale for its supplementation is that they are essential for synthesizing protein, replacing nitrogen losses, and preventing further skeletal muscle breakdown.

1. Calorie value and preparations

When an amino acid is oxidized for energy, it provides 4 calories per gm. 6.25 gm of protein contains 1 gm of nitrogen. The standard amino acid solution contains approximately 40–50% essential amino acids (N=9) and the rest 50–60% nonessential amino acids (N=10) plus semi-essential (N=4) amino acids. Crystalline amino acid solutions used in PN are of high biological quality. Standard commercially made crystalline amino acid formulations are available in 3 to 15% concentrations. 10% solution of amino acids contains 100 gm of protein per liter.

2. Requirements

Approximately 15 to 20% of total energy requirements should come from protein. Protein and energy requirements are closely related. To minimize protein catabolism, a sufficient amount of non-protein calories, such as carbohydrates and fats, must be administered simultaneously. A calorie to nitrogen ratio of 100–150:1 will be satisfactory for normal patients. The protein requirement for an average stable adult is about 0.8–1.5 gm/kg/day. When patients receive protein without adequate calories, the requirement for protein increases because, in addition to its use for protein synthesis, the protein supplied is also utilized for energy production. Amino acid administration is essential to prevent protein-energy malnutrition (PEM). PEM may lead to immunosuppression and infection in critically ill patients.

Protein requirement is higher (1.5–2.5 gm/kg/day) in massive burns, severe trauma, hypoproteinemia, protein-losing enteropathy or nephropathy, or in patients receiving dialysis treatment. In critically ill patients with sepsis, a large amount of nitrogen loss results from abnormal metabolism. General guidelines for protein requirement in hospitalized patients are summarized in Table 55.7 [13].

Table 55.7 Recommended daily protein intake

Clinical condition	Protein requirements (gm/kg ideal body wt/day)
Stable	0.8–1.5
Critically ill, trauma, sepsis	1.2–2.5
Acute kidney injury (undialysed)	0.8–2.0
Renal replacement therapy	Additional 0.2 gm/kg/d, up to 2.5 gm/kg/d
Burns	1.5–2.0
Hepatic failure	1.2–2.0
Traumatic brain injury	1.5–2.5

For critically ill patients, optimal protein intake is approximately 1.5 gm/kg/day. This amount of protein intake can decrease the degree of nitrogen loss in catabolic patients, mostly by enhancing visceral protein synthesis and, to a lesser extent, by diminishing peripheral protein catabolism. Delivering an additional amount of protein does not further reverse this trend and does not yield a positive nitrogen balance. On the contrary, if excess protein (>1.7 gm/kg/day) is provided, it results in excess ureagenesis rather than contributing to protein anabolism.

3. Functions and advantages

- Protein synthesis: The main function of protein is the growth and maintenance of cells and tissues in a steady stage.
- Reduces the rate of protein catabolism: In critically ill patients, protein catabolism exceeds protein synthesis and leads to net protein loss. Administration of an adequate amount of protein along with calories decreases body protein loss but does not prevent the loss completely.
- Calorie supplementation: 1 gm of protein provides 4 kcal energy. Patients receiving inadequate calories from carbohydrates and lipids will utilize protein for energy production. Thus, excess protein is needed for nitrogen balance when energy intake is low.

4. Contraindications and adverse effects

- Hepatic insufficiency: In patients with hepatic insufficiency, infusion of standard amino acids may cause metabolic alkalosis, increased levels of ammonia, stupor, or coma.
- Renal failure: A patient with impaired renal function may develop a marked rise in BUN.
- Metabolic or respiratory alkalosis may be exacerbated by the excess acetate ions present in amino acid solutions.
- Rapid administration may cause nausea, vomiting, headache, chills, or fever.
- Administration of excess protein or insufficient calorie supplementation results in the production of an increased amount of urea. Renal loss of excess nitrogen leads to water loss and may cause hypertonic dehydration (especially in young children) unless extra water is provided.

5. Monitoring

In stable patients receiving an amino acid infusion, the adequacy of protein support can be assessed by analyzing nitrogen balance.

Nitrogen Balance =
Nitrogen Intake - Nitrogen Loss

Nitrogen Intake =
Protein Intake [gm] / 6.25

Nitrogen Loss = 24-Hour UUN + 4

Where 24-hour UUN represents the gm of nitrogen excreted in the urine over 24 hours, and the addition of + 4 accounts for 4 gm of nitrogen lost each day as insensible losses via the skin and gastrointestinal tract.

Positive nitrogen balance suggests anabolism or nitrogen retention. Nitrogen loss greater than nitrogen intake (negative nitrogen balance) suggests net nitrogen loss. If the blood urea nitrogen (BUN) level exceeds 100 mg/dL or a patient with hepatic encephalopathy shows clinical worsening with a rising ammonia level while infusing amino acids, the dose of standard amino acids needs to be reduced or discontinued [24].

6. Example of calculation of protein/amino acid solution requirements

Example: For a 60 kg male with 1.0 gm per kg per day protein requirements, considering basic requirements and adding stress factors, how much amino acid solution is needed for PN in a day?

- Total daily protein requirements will be 60 kg × 1.0 gm/kg = 60 gm per day.
- 100 ml solution of 5% and 10% of amino acid preparation provides 5 gm and 10 gm of amino acid, respectively. So, to provide 60 gm of amino acid/day required volume of 5% and 10% of amino acid preparations will be 1200 and 600 ml/day, respectively.

E. Lipids

Lipid injectable emulsions (ILEs, formerly known as Intravenous Fat Emulsion) are an essential component of PN formulations that have two main functions: to provide an energy-dense source of calories that help in reducing the dextrose load needed to meet energy goals and supply essential fatty acids (EFAs) such as linoleic and linolenic acids which prevent or correct essential fatty acid deficiency.

1. Contents of lipid emulsion

Different lipid emulsions contain varying amounts and proportions of omega-3, omega-6, and omega-9 fatty acids. Lipid emulsions containing soybean oil are the mainstay and the first-generation lipids for parenteral nutrition and have been used extensively with fair success for decades [25, 26]. This formulation for PN also contains three other components: egg yolk phospholipids as an emulsifying agent to mix two immiscible liquid phases, fine droplets of oil suspended in water; glycerin to make the formulation isotonicity with plasma; and sodium hydroxide, which adjusts the final pH around 8.0 [27, 28].

First-generation soybean oil containing lipid emulsions are composed mainly of omega-6 FA-rich linoleic acid with low content (about 10%) of omega-3 FA containing α-linolenic acid (ALA), and therefore has a high (7:1) omega-6/omega-3 FAs ratio. The high content of omega-6 FA in soybean-based lipid emulsions has pro-inflammatory and immunosuppressive harmful effects and therefore is associated with adverse outcomes in critically ill patients [25, 29, 30].

Alternative lipid emulsions, such as generation 2 (combining soybean oil with medium-chain triglycerides), generation 3 (using olive oil), and generation 4 (using fish oil) lipid emulsions, have been developed to decrease the harmful effects of the omega-6-rich linoleic acid content and to lower the ratio of omega-6 to omega-3 fatty acids as summarized in Table 55.8 [26, 31–33].

2. Caloric values, preparations, and requirements

Lipid is the richest source of calories; 1 gm of lipid provides 9 kcal (vs. dextrose provides 3.4 kcal/gm and protein provides 4.0 kcal/gm). The lipid emulsions are available as 10% (1.1 kcal/ml), 20% (2.0 kcal/ml), and 30% (3.0 kcal/ml) solution and have low osmolarity (260 mOsm/L). The use of 30% lipid emulsion is approved for preparing a total nutrient admixture or "3 in 1" delivery system in a pharmacy admixture program. Still, it is not recommended for direct intravenous administration.

In PN, lipids should be infused to provide about 25–40% of non-protein calories [34]. ILE requirements are 1 gm/kg/d in stable patients and less than 1 gm/kg/d in critically ill, trauma, and sepsis patients (ASPEN 2019) [13]. Lipid emulsions should be started usually

Table 55.8 Classification, composition, and benefits of lipid injectable emulsions

Generation of ILEs	Composition of ILEs	The ratio of ω-6:ω-3 FAs	Rationale and benefits	Selected ILEs products
First	100% soy oil	7:1	Used to supply EFA and energy	Intralipid, nutrilipid
Second	50% soy oil, 50% MCT	7:1	MCT is added to reduce the soy content and the amount of ω-6 FA	Lipofundin MCT/LCT
Third	20% soy oil, 80% olive oil	9:1/NA	Reduce the soy content. Less prone to inflammatory processes and immune suppression	ClinOleic/clinolipid
Fourth	30% soy oil, 30% MCT, 25% olive oil, 15% fish oil	2.5:1	Reduce the soy content, ω-6 to ω-3 FA ratio, infectious complications, and hospital stay. Preferred in critically ill and surgical patients	SMOFlipid

EFA: Essential fatty acid; FA: Fatty acid; ω-3, Omega 3; ω-6, Omega 6; ILE: Lipid injectable emulsion; LCT: Long chain triglycerides; MCT: Medium-chain triglyceride; MUFA: Monounsaturated fatty acid; Soy: Soybean

at a dose of 0.7 gm/kg/day, the upper recommended dose is 1 gm/kg/day, and it should not exceed 1.5 gm/kg/day (ESPEN 2019) [18]. In obese patients, underfeeding help in the mobilization of the endogenous fat store and, as a result, improves insulin sensitivity and glycemic control [35].

3. Functions and advantages

- Dense calorie supplementation: IV lipid emulsion is a concentrated calorie source (9 kcal/gm), so it is the other major calorie-rich fuel that provides energy effectively. Providing more energy in a given volume (compared to IV dextrose fluids) is an essential advantage of lipid emulsion in critically ill, volume overloaded patients.
- Avoids hyperglycemia: Lipid emulsion provides a portion of the total calorie requirement, thereby allowing a lower rate of dextrose infusion and reducing the potential adverse effects of infusing excess glucose for calories.
- Protein sparing effect: IV lipid emulsion is more effective than IV dextrose in providing energy. In PN, adequate supplementation of calories by curtailing protein oxidation prevents protein catabolism and exerts a protein-sparing effect.
- Less CO_2 production (lower respiratory quotient): Compared to carbohydrates, lipids produce less CO_2 and, therefore, are preferred in respiratory compromised patients. Lipids' respiratory quotient (RQ) is the least (RQ of lipids 0.7 vs. 0.8 for proteins and 1.0 for carbohydrates). The respiratory quotient is the ratio of CO_2 production to O_2 consumption.
- So, IV lipid emulsion has the advantages of better glucose tolerance, less hyperinsulinemia, less fatty infiltration of the liver, and less production of CO_2. Because of these benefits, lipid emulsion is widely utilized in patients with hyperglycemia, diabetes, liver disease, and respiratory failure.
- Prevention of essential fatty acid deficiency: Lipid emulsion assists in wound healing, the production of red blood cells (RBC), and prostaglandin synthesis. PN administration without

Table 55.9 Advantages of lipid emulsion in PN solutions
• Large amount of calories in a small volume.
• Improve glucose tolerance and reduce insulin levels.
• Reduces the risk of refeeding syndrome.
• Lower osmolarity. Reduces the risk of thrombophlebitis. Safe for PPN.
• Supply of essential fatty acid.
• Less CO_2 production than glucose oxidation, which is beneficial in respiratory compromised patients weaning from ventilator support.

lipid supplementation for more than 2 weeks should be avoided because it can lead to essential fatty acid deficiency, causing dry, scaly skin rash, hair loss, thrombocytopenia, anemia, poor wound healing, and increased susceptibility to infection. To prevent essential fatty acid deficiency, supplement about 2% to 4% of total caloric intake as linoleic acid and 0.25% to 0.5% as alpha-linolenic acid beyond 2 weeks of administering PN.

- Reduced risk of thrombophlebitis due to lower osmolality: Hypertonic solutions are irritant to veins, thus increasing the risk of thrombophlebitis. Unlike the hypertonic dextrose solutions, the osmolarity of lipid emulsion is low (260 mOsm/L), almost the same as that of plasma. So the addition of lipid emulsion reduces the osmolarity and, therefore, reduces the risk of thrombophlebitis due to PN. Besides, lipid emulsion exerts a protective effect on vascular endothelium. For the same reason, lipid emulsion is an important component of solutions for peripheral parenteral nutrition (PPN).

The advantages of including lipid emulsion in PN are summarized in Table 55.9.

4. Adverse effects and disadvantages

The adverse effects of lipid administration are:

- Increased triglyceride levels: Infusion of lipid emulsion causes an increase in plasma triglycerides, cholesterol, phospholipids, and concentration of lipoproteins. When lipid emulsion is infused rapidly and/or in high doses, the rate of infusion of triglyceride exceeds the rate of hydrolysis of triglyceride by endothelial enzyme lipoprotein lipase and, therefore, can cause hypertriglyceridemia [36].
- Sepsis: Lipid emulsion carries a risk of infection when administered separately over a prolonged time.
- Fat embolism: Lipid is less stable when infused with amino acids and glucose as a combined "three-in-one solution". Destabilized particles of fat coalesce into larger droplets and subsequently form fat emboli. For the same reason, a three-in-one solution has a shorter storage life, and improperly mixed or delayed in the use of solution carries the risk of fat embolism.
- Less frequent complications: Immediate or early adverse reactions include dyspnea, cyanosis, nausea or vomiting, headache, allergic reactions, chest and back pain, or thrombocytopenia. Delayed complications with prolonged administration include hepatic dysfunction, fat overload syndrome, pancreatitis, and delayed gastric emptying.

Most adverse effects are instead due to hypertriglyceridemia than due to lipids per se. Hypertriglyceridemia occurs due to the infusion of lipids at a rate faster than lipid clearance. Thus, if lipids are infused at proper infusion rates and serum triglycerides are monitored regularly, most adverse effects of lipids are avoided.

5. Indications

Lipid administration is indicated in all patients needing a home or prolonged PN. Lipid administration is also indicated in patients who need PPN, high caloric supplementation but fail to tolerate carbohydrates, critically ill patients, and patients with hyperglycemia, diabetes mellitus, and respiratory failure.

6. Contraindications

Avoid lipid emulsion in patients with severe hypertriglyceridemia (reduce dose if serum triglycerides >400 mg/dL and do not use if serum triglycerides >1000 mg/dL), in patients who are at risk of developing fat embolism, hypersensitivity to lipid emulsion, severe metabolic acidosis, in patients with acute shock, anemia, severe coagulopathy, and evidence of intravascular coagulation [34]. In addition, lipid emulsions should be used cautiously in obese patients because of the greater risk of hyperglycemia and hypertriglyceridemia.

7. Administration and monitoring

IV lipid emulsion used to prevent essential fatty acid deficiency is given 3 to 4 days a week; while used as a calorie source, it is provided daily. The lipid can be administered IV either separately by piggyback infusion with the 2-in-1 system (containing dextrose and amino acids) or as 3 in 1 admixture (all-in-one infusion) of dextrose, protein, and lipids in a single bag. Lipid emulsions may also provide rich media for the growth of bacteria and fungi. Therefore, scrupulous handwashing before handling lipids is mandatory to reduce the risk of touch contamination. As exposure of the lipids to light causes the formation of potentially toxic peroxides, avoid it by wrapping it in aluminum foil or carbon paper.

Since most complications are associated with rapid IV lipid infusion (greater than 1.0 kcal/kg/hr or 0.11 gm/kg/hr), the rate should not exceed 0.7 kcal/kg/hr. Usually, lipid emulsions should be administered slowly over 12 hours. However, avoid a prolonged infusion of lipids and discard bottles and tubing hung alone after 12 hours. PN solution bag may hang for a maximum of 24 hours and discard any remaining solution and tubing after 24 hours [37].

In patients with lipid infusion, triglyceride levels should be monitored at least weekly. Lipid infusion should be reduced or discontinued if the triglyceride level exceeds 400 mg/dL to decrease the risk of pancreatitis or decreased diffusion capacity in patients with severe chronic obstructive lung disease.

8. Selection of lipid emulsions (ILE)

The most commonly used soybean based first-generation lipid emulsions are usually recommended for short-term use (<2 weeks) in stable critical patients with normal LFTs [33].

Newer lipid emulsions for PN are developed which has a lower content of harmful omega-6 FA and contains omega-3 FA in a higher amount [31]. In contrast to omega-6 FA, omega-3 FA-enriched newer lipid emulsions (i.e., fish oil containing ILE) has beneficial anti-inflammatory and immunomodulatory effects, which reduces the risk of infection and sepsis and shorten ICU and hospital stay and therefore preferred in high-risk patients requiring PN such as sepsis, critically ill and surgical patients [33, 38–40]. Lipid emulsion preparation containing a mixture of soybean oil, medium-chain triglycerides (MCTs), olive oil and fish oils, such as SMOF lipid is available commercially [41].

9. Example of calculation of lipids/lipid emulsion requirements

Example: For a 60 kg male with 25 kcal/kg/d energy requirements, how much lipid emulsion is needed (considering 30% of total energy requirement in the form of lipid) in a day?

- Total caloric requirements will be 60 × 25 = 1500 kcal/day, and lipid requirement will be 450 (30% of 1500) kcal/day.
- 10% and 20% of lipid emulsions provide 1.1 kcal/cc and 2.0 kcal/cc, respectively. So, to provide 600 kcal/day required volume of 10% and 20% of lipid emulsion will be about 409 ml (450 ÷ 1.1) and 225 ml (450 ÷ 2.0) respectively.

F. Diseases-specific amino acids

Modified specialized solutions with adjusted amino acid contents are available for the specific disease state.

1. For hepatic encephalopathy

Specific "hepatic formula" for parenteral nutrition is a modified amino acid solution rich in branched-chain amino acids (BCAAs) (valine, leucine, and isoleucine) and has a low content of aromatic amino acids (AAA) (phenylalanine, tryptophan, and tyrosine), and sulfur-containing amino acids like methionine [42].

Potential mechanisms by which branched-chain amino acids benefits are:

- Compared with non-branched chain amino acids (Non-BCAAs), which are metabolized by the liver, BCAAs are uniquely oxidized chiefly in skeletal muscle and adipose tissues (and not in the liver). BCAAs enhances detoxification and removal of ammonia in skeletal muscles, reduces plasma ammonia concentration, and may reduce hepatic encephalopathy [43].
- In hepatic insufficiency due to liver cirrhosis, high aromatic amino acids (AAA) and low BCAAs/AAA ratio play an important role in developing hepatic encephalopathy [44]. BCAAs and aromatic amino acids are transported into the brain via the same carrier [45]. So, BCAAs compete with aromatic amino acids, potentially decreasing the passage of aromatic amino acids across the blood-brain barrier, reducing the release of neurotransmitters, notably serotonin, and thereby having beneficial effects on brain function [46, 47].

A high concentration of BCAAs (35–45%) in "hepatic formula" corrects the amino acid imbalance and is recommended in selected patients of liver cirrhosis with hepatic encephalopathy grades III–IV refractory to standard management [42].

BCAAs-enriched formulations show highly significant improvement in mental recovery [48, 49], but no evidence suggests improvement in the patient's outcome [4, 49].

Because of increased cost and controversial efficiency, BCAAs should not be used as the first-line treatment for hepatic encephalopathy [4].

In patients with liver diseases, use standard amino acid (and reduce the cost of therapy) in the absence of encephalopathy, grades I or II hepatic encephalopathies, once the encephalopathy resolves, and for preoperative nutrition after liver transplantation [50].

2. For acute kidney injury (AKI)

Supplementation of protein leads to accumulation of end products such as urea with worsening of uremia. Therefore, protein restriction was previously practiced to reduce uremic symptoms and avoid or delay initiating dialysis therapy. But as per current recommendations, protein restriction should be avoided in patients with renal insufficiency [4, 51].

Recommended doses of protein in non-dialysis AKI patients are 0.8−1.0 gm/kg/day in non-catabolic AKI [51], and in AKI patients on renal replacement therapy (RRT) are 1.0–1.5 gm/kg/d as per KDIGO guidelines (2012) [51], or additional protein 0.2 gm/kg/day, up to 2.5 gm/kg/day as per ASPEN guidelines (2016) [4].

The role of specially designed amino acid-containing solutions ("nephro-solutions") is controversial but may benefit patients who do not require dialysis [52].

G. Immunomodulators

Immunonutrients are specific nutrients that have the potential to modify inflammatory or immune responses with beneficial effects on mucosal barrier function, cellular defense, and local or systemic inflammation [53]. The use of immune-modulating nutrients such as glutamine, arginine, and omega-3 fatty acids are common. However, a recent Cochrane Database Systematic Review (2019) found the effect of these immunonutrition supplements on the duration of ventilator days, ICU length of stay, or oxygenation in patients with acute respiratory distress syndrome to be uncertain [54].

1. Glutamine

Glutamine is the body's most abundant amino acid, which is primarily synthesized by skeletal muscles. glutamine is the primary energy source for rapidly dividing cells such as intestinal epithelial cells, vascular epithelial cells, and proliferating immune cells. Glutamine is vital for maintaining the gut barrier function and is considered a "fuel for the immune system," which exerts antioxidant and cytoprotective effects, helps defend the body against pathogens, and decreases infectious complications [55].

Studies in septic and critically ill patients have shown that administering glutamine does not improve outcomes such as mortality, organ failure, infectious complications, or length of stay [56–58]. Some studies have even shown harmful effects [58–60], leading to the recommendation against administering glutamine in septic critically ill patients [61]. In recent guidelines, parenteral glutamine is not recommended in critically ill, unstable, and complex ICU patients and with multiorgan failure, especially with liver and renal failure (Canadian guidelines 2015, ASPEN guidelines 2016, ESPEN guideline 2019) [4, 18, 62].

As clinical benefits of parenteral glutamine are documented in various studies [63–67], IV glutamine may be used in selected patients on PN who are stable, together with adequate parenteral energy and protein after excluding hemodynamic instability, hepatic or renal failure [68].

Parenteral glutamine supplementation is preferred over enteral for patients in the intensive care unit [69]. When IV glutamine supplementation is indicated in PN, the recommended dose of glutamine is 0.2–0.4 gm/kg/day (0.3–0.6 gm/kg/day of alanyl-glutamine dipeptide) [70].

2. Omega 3 fatty acids

Omega-3 fatty acids have anti-inflammatory and immunomodulatory effects and have been shown to improve clinical outcomes in surgical, trauma, cancer, and critically ill patients, as well as during long-term parenteral nutrition due to their inflammation-resolving effects [29, 30, 71].

Administration of injectable lipid emulsion containing omega-3 fatty acids provides significant benefits such as the reduction in risk of infection, sepsis, and length of stay in both ICU as well as hospital, and therefore is preferred over standard lipid emulsions (without omega-3 fatty acids) in hospitalized adult patients requiring PN [30, 40, 71].

Omega-3 fatty acids are abundant in fish oil. Newly designed **SMOFlipid** solution is a **S**oybean oil (30%), **M**edium-chain triglycerides (30%), **O**live oil (25%), and **F**ish oil (15%) containing **lipid** emulsion, which is used to provide omega-3 fatty acids enriched PN [26]. The higher cost of omega-3 fatty acids enriched lipid emulsions is a concern. But improved clinical outcomes (reduced infectious complications and shorter hospital and ICU stays) offset the overall costs [72, 73].

3. Arginine

Arginine is a nutrient that boosts the immune system and is considered a nonessential amino acid under normal circumstances. However, during times of catabolism, it becomes a conditionally essential nutrient. Arginine plays an essential role in protein synthesis, nitric oxide generation, and immunomodulation, thereby playing a major role in cellular defense and wound healing. In addition, arginine supplementation reduces the rate of infectious complications and the duration of hospitalization postoperatively [74].

Intravenous or enteral arginine supplementation as a standalone treatment is not recommended for critically ill patients or those with severe sepsis [4, 75, 76]. For patients requiring enteral nutrition therapy, an immune-modulating formula containing both arginine and fish oils should be used in the perioperative or postoperative period, including in malnourished patients undergoing major cancer surgery and in severe trauma cases in the SICU [4, 76].

H. Micronutrients

Electrolytes, trace elements, and vitamins come under micronutrients. Requirements of micronutrients for PN in the normal adult are summarized in Table 55.10. The minerals and vitamins required in parenteral nutrition are much lesser than in enteral nutrition because of better bioavailability with direct intravenous infusion. These value needs to be modified considering the clinical situations.

I. Electrolytes

As electrolytes are essential to perform critical metabolic activities, it is a must in all PN formulas. As sodium influences intravascular volume status, it is restricted in patients at risk of volume overload (e.g., cardiac, liver, and renal failure) and given liberally when volume expansion is desired (those with GI losses). Potassium requirement increases in patients with increased renal loss of potassium, in those who receive amphotericin B therapy, and in severely malnourished patients while initiating PN.

After meeting phosphate requirements, sodium and potassium cations are usually added to parenteral nutrition solutions in the form of chloride or acetate salts. The choice of the salt form has an impact on acid-base balance. The liver metabolizes acetate into bicarbonate, which acts as an alkaline buffer. Therefore, acetate is a preferred salt in patients with metabolic acidosis. Loss of a large amount of chloride (such as nasogastric aspiration) can cause metabolic alkalosis. Sodium and potassium are provided in such patients, preferably as chloride salt for PN.

Table 55.10 Recommended daily parenteral requirements of micronutrients

Nutrient	Requirements	Nutrient	Requirements
Electrolytes		**Fat soluble vitamin**	
Sodium	1.0–2.0 mEq/kg	Vitamin A	990 mcg (3300 IU)
Potassium	1.0–2.0 mEq/kg	Vitamin D	5.0 mcg (200 IU)
Magnesium	8.0–20 mEq	Vitamin E	10 mg (10 IU)
Phosphate	20–40 mmol	Vitamin K	150 mcg
Calcium	10–15 mEq	-	-
Trace minerals		**Water soluble vitamins**	
Chromium	≤10 mcg	Thiamine (B1)	6.0 mg
Copper	0.3–0.5 mg	Riboflavin (B2)	3.6 mg
Manganese	55 mcg	Niacin (B3)	40 mg
Selenium	60–100 mcg	Pantothenic acid (B5)	15 mg
Zinc	3.0–5.0 mg	Pyridoxine (B6)	6.0 mg
-	-	Folic acid (B9)	600 mcg
-	-	Cobalamin B12	5.0 mcg
-	-	Ascorbic acid (Vit C)	200 mg
-	-	Biotin	60 mcg

The use of sodium bicarbonate in PN is incompatible as it forms insoluble coprecipitates, mainly with calcium and magnesium. Thus, bicarbonate salts should never be infused through a common intravenous line with PN.

J. Trace elements

Trace elements, in small amounts, are crucial for efficient substrate utilization and other supporting functions and therefore are an essential component of PN. A deficiency of trace elements develops quickly in stressed patients or patients with increased GI losses.

On the other hand, stable patients do not develop evidence of deficiency, even though trace elements are not supplemented for about two months. Commercial preparations are available as injections in various combinations, providing required trace elements.

Most trace element PN formulations contain zinc, copper, chromium, manganese, and selenium but do not have iron and iodine [13]. Selenium supplementation is recommended for patients receiving long-term PN because of the risk of muscle weakness and fatal cardiomyopathy caused by selenium deficiency.

The daily requirement of iodine is 70–150 mcg and 1 mg of elemental iron, but most PN formulations do not contain these trace elements. In most patients receiving PN, iron is not supplemented because of adequate body storage. Note that iron is not generally part of commercially available standard additives and not added to PN solutions because it can cause lipid emulsions to destabilize and therefore is incompatible with lipid-containing PN formulas like "3 in 1" solutions. In addition, iron is not given routinely to patients who are critically ill because free iron may promote bacterial growth and increase susceptibility to infection [77].

The requirements for many trace elements in PN are lower than for oral or enteral nutrition. This is because the gut absorbs only a portion of the supplemented nutrient, sometimes less than 10% (e.g., chromium).

However, it is important to remember that some trace elements' parenteral requirements are higher than actual body requirements. These increased requirements result from increased urinary losses, as they are delivered via systemic rather than portal circulation (and therefore not captured by the liver).

K. Vitamins

Vitamins are essential for normal metabolism and are an important part of PN. Requirements of trace elements for PN are generally lower than in EN, but the reverse is true for vitamins.

Parenteral requirements of vitamins are higher than those required through oral or enteral administration due to the following reasons.

- Vitamins supplemented orally are generally absorbed much more than most trace elements.
- Vitamins get degraded during preparations and storage. For example, vitamin A, riboflavin, and vitamin K are degraded by light, and thiamine is degraded by sulfite ions used as a preservative for amino acid solutions.
- Vitamins are lost partially due to adherence to tubing and delivery bags.

The recommended dose for water-soluble vitamins is four to five times the usual and minimum daily requirements for fat-soluble vitamins. Commercially available aqueous multivitamin preparations will provide normal daily requirements for most vitamins except for vitamin K.

Commercially available aqueous multivitamin preparations will provide normal daily requirements. Vitamin K is beneficial to most patients on PN and is administered as multivitamin preparation or added separately to lipid emulsions, but it may be detrimental to patients receiving oral anticoagulants [78, 79]. It is important to remember that vitamins and trace elements are added to PN shortly before use because of the concern about stability.

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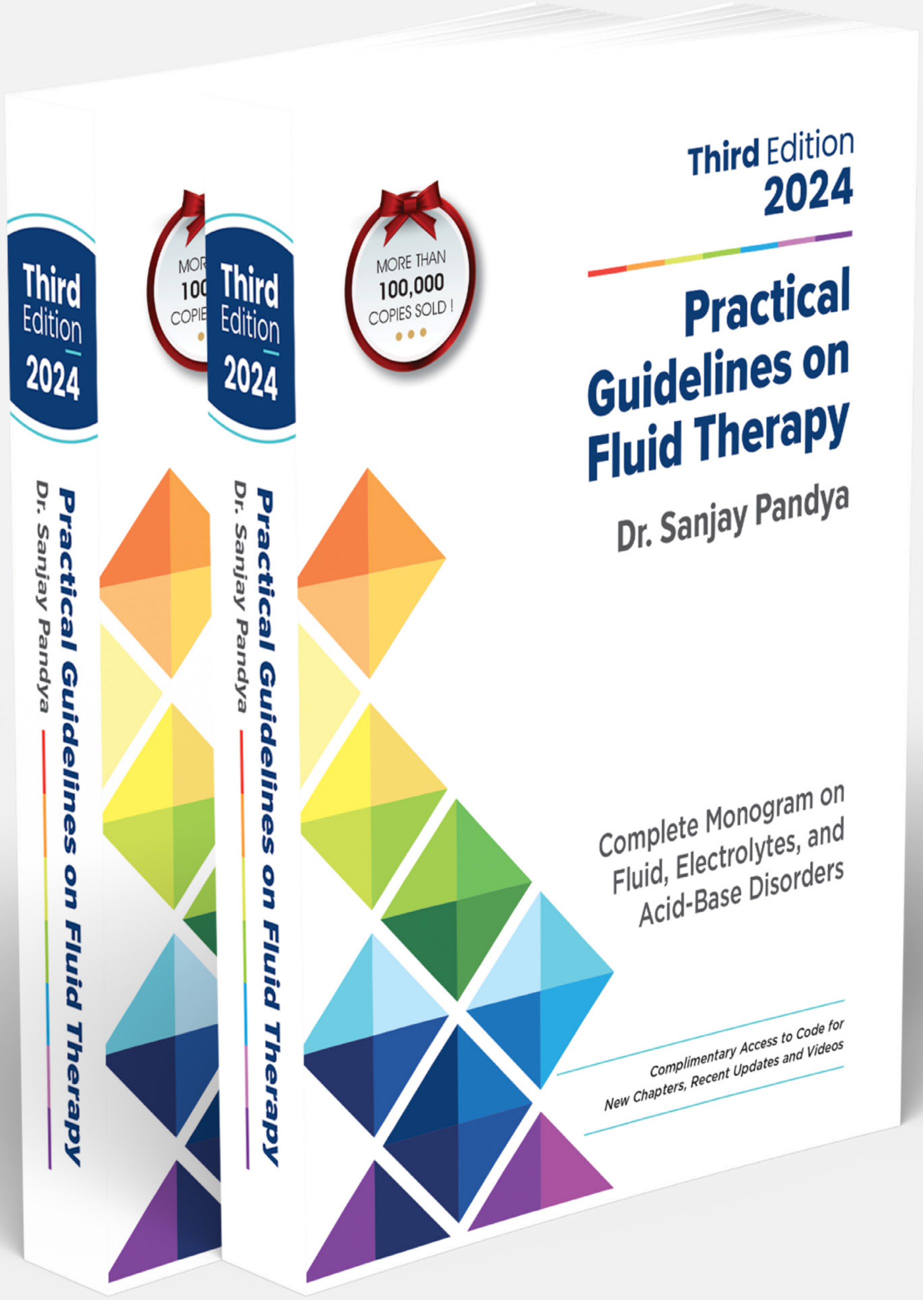
Chapter 56:

Parenteral Nutrition in Specific Diseases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56 Parenteral Nutrition in Specific Diseases

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In specific diseases, individuals have nutritional needs that differ from the usual guidelines, necessitating a personalized nutritional strategy. These conditions require a tailored nutritional approach to meet their distinct requirements. This chapter will discuss the unique nutritional considerations, goals, indications, timing for initiating parenteral nutrition, nutritional requirements, and management of several common disorders.

ACUTE KIDNEY INJURY (AKI)

Nutritional considerations

In acute kidney injury, the rapid decline in kidney function not only leads to water, electrolyte, and acid-base disturbances but also affects carbohydrate, protein, and lipid metabolism and significantly affects nutrition. In AKI, excessive protein catabolism and inadequate intake of nutrition lead to protein-energy wasting (PEW) and malnutrition.

Malnutrition is common in hospitalized patients with AKI, is a poor prognostic marker, and is a significant predictor of morbidity and mortality in AKI [1–4]. In addition, patients with AKI given low calories and amino acids are associated with higher hospital mortality [5]. So, do not restrict protein intake in AKI patients to avoid or delay the initiation of dialysis [6, 7].

Goal, indications, and timing for initiation of parenteral nutrition (PN)

The general goals of nutrition support are to prevent malnutrition, maintain nutritional status, and limit the complications of AKI by providing adequate amounts of energy, protein, and nutrients.

AKI patients with mild catabolism can be fed orally. Moderate to severely catabolic patients with AKI need nutritional support, and enteral nutrition is the preferred route in such patients. However, total or supplementary PN has indicated if enteral nutrition is inadequate or cannot be given in patients with significant gastrointestinal (GI) dysfunction [8].

When to initiate PN in patients with AKI is an important question to be answered. Early PN may delay recovery in AKI and prolong the duration of renal replacement therapy due to substantial catabolism of the extra amino acids leading to higher levels of plasma urea and, therefore, should be avoided [9].

Compared with early initiation, late initiation of PN is associated with rapid recovery and lesser complications in critically ill adults [10]. Recent ESPEN guidelines (2019) recommended starting PN within three to seven days and providing half of the predicted or measured energy need in the beginning [11].

Nutritional requirements and management

Nutritional requirements of AKI depend on various factors such as underlying disease, associated comorbidities, the need for renal replacement therapy (RRT), including its type and frequency, and pre-existing nutritional status, as summarized in Table 56.1.

1. AKI treated conservatively (non-dialytic therapy)

- **Energy requirements:** It varies as per the clinical status of patients with AKI.

  Energy required for uncomplicated AKI is in any stage is 20–30 kcal/kg/day, which is similar to that required by a normal adult individual [7, 12].

  Energy requirement increases (about 25 to 35 kcal/kg/day) in critically ill patients with AKI (e.g., severe sepsis, respiratory failure, burns, and multi-organ failure) [13, 14] and during continuous renal replacement therapy (CRRT) [15].

  Providing higher calories does not improve patients' outcomes in AKI [16]. In AKI patients, indirect calorimetry is the standard and clinically recommended method to calculate energy requirements which helps to avoid overfeeding.

Table 56.1 Guidelines for nutritional requirements in acute kidney injury

Nutritional requirements	ESPEN 2006	KDIGO 2012	ASPEN 2016
Energy	20–30 kcal/kg/d	20–30 kcal/kg/d	25–30 kcal/kg/d
Protein			
Noncatabolic AKI without dialysis	0.6–0.8 gm/kg, max. 1.0 gm/kg	0.8–1.0 gm/kg	1.2–2 gm/kg
RRT, in hypercatabolism	1.0–1.5 gm/kg	1.0–1.5 gm/kg for RRT, up to 1.7 gm/kg for CRRT	Additional 0.2 gm/kg up to 2.5 gm/kg
Carbohydrates	3–5 gm/kg (max. 7 gm/kg)	-	-
Lipid	0.8–1.2 gm/kg (max. 1.5 gm/kg)	-	-

- **Protein requirements:** Protein requirements in AKI needs due attention as it is variable based on the condition of the individual patient (Table 56.1). Protein requirements recommended for patients of AKI, not on dialysis is 0.8−1.0 gm/kg/day for stable, non-catabolic patients (KDIGO 2012) and 1.2–2 gm/kg for critical ICU patients (ASPEN 2016) [6, 7]. Avoid supplementation of the greater amount of protein in AKI because retention of nitrogenous waste will aggravate uremic complications and can also contribute to acidosis [7].
- **Non-protein caloric supplements:** In AKI receiving PN, carbohydrates, and lipids represent about 65–70% (3 to 5 gm/kg/d) and 30–35% (0.8 to 1.0 gm/kg/d) of the calorie intake of total non-protein energy supply respectively [7, 17].
- **Fluid and electrolytes requirements:** Adjust/restrict fluid intake as per the urine output to avoid volume overload in oliguric patients. Most of oliguric patients also need sodium restriction. Maximally concentrated PN solutions are infused through a central line in oliguric patients. Avoid hyperkalemia, hypermagnesemia, and hyperphosphatemia by restricting potassium, magnesium, and phosphorus in PN.

2. AKI treated with renal replacement therapy

A large amount of amino acids is lost into the effluent fluid during RRT, and its variable depending on the type of modality (i.e., the approximate amount of amino acid lost is about 3−6 gm during conventional hemodialysis, 7−10 gm during sustained low-efficiency dialysis (SLED), and 14−22 gm per session during continuous venovenous hemofiltration (CVVH) respectively [18]. To compensate for the protein loss, protein replacement KDIGO recommended are 1.0–1.5 gm/kg/d for AKI on intermittent RRT and up to 1.7 gm/kg/d in patients on continuous renal replacement therapy (CRRT) [7]. To replace a significant loss of amino acid in CRRT, it is recommended to increase protein intake to a range of 1.5–2.5 gm/kg/day [6, 14, 19].

BURNS

Nutritional considerations

Malnutrition in patients with burns carries a high risk of complications such as infection and delayed wound healing and therefore is very important in managing moderate-to-severe burn injury.

Important causes of malnutrition in burns are:

- Loss of protein and micronutrients as the skin barrier is lost.
- Increased energy expenditure to overcome heat loss through the exposed surface and to maintain body temperature.
- Persistent and prolonged post-burn hypermetabolic state and increased catabolism.

Feeding route: In burn patients, enteral nutrition (EN) is recommended over PN because of the advantages of early EN, such as protection of the gastrointestinal tract, improved nutrient adequacy, reduction in rates of complications, infection, length of hospital stay, cost, morbidity, and mortality [20, 21]. EN is preferred, and PN is not recommended routinely in burns because of adverse effects like overfeeding, impaired immunity, liver failure, and higher mortality [22]. PN is administered in burn patients only when EN is not feasible, not tolerated, or inadequate to meet with desired total nutrient requirements [6].

Nutritional requirements and management

Energy requirements: In patients with burns, nutritional support is provided to meet increased energy requirements due to the hypermetabolic state without causing overfeeding [23]. Indirect calorimetry is the standard and preferred method to determine energy requirements in burns [6]. However, different equations used to determine energy requirements in burns are less reliable because they overestimate or underestimate caloric requirements [24]. When indirect calorimetry is not available or feasible, alternatively Toronto equation is recommended in adults [20].

Protein requirement: Protein requirement is significantly higher in burns because of the need for protein for wound healing, immune function, to replace ongoing losses, and to reduce protein catabolism [23]. ESPEN (2013) and ASPEN (2016) guidelines recommend 1.5 to 2 gm protein/kg/day in adults [6, 20].

Carbohydrate requirement and glycaemic control: Administer carbohydrates to provide up to 60% of total energy intake from nutrition and non-nutritional sources [20]. However, carbohydrate administration carries the risk of hyperglycemia, and poor glucose control adversely affects outcomes in burns [25]. So, while infusing carbohydrates, monitor blood glucose levels closely, and keep glucose levels under 144 mg/dL (and over 81 mg/dL), preferably by continuous intravenous insulin infusion to achieve tight glycemic control.

Lipid requirement: Administer lipids to provide <35% of total energy intake from fat and monitor total fat delivery [20].

As metabolic demands are high in patients with severe burns, administration of PN via central venous access is preferred.

Glutamine and micronutrients requirement: Supplementation of 0.3 gm/kg/day glutamine is beneficial. Patients with major burns have increased micronutrient requirements due to hypermetabolism, wound healing requirements, and cutaneous exudative losses and need an early supplementation with supra-nutritional amounts of zinc, copper, selenium, and vitamin B1, C, D, and E to prevent deficiency-related complications [20].

CANCER

Cancer-related malnutrition (CRM), weight loss, and cachexia occur in 30 to 80 percent of cancer patients, which contribute to excess morbidity and mortality [26, 27].

Malnutrition reduces the benefit of cancer therapy, increases chemotherapy-related toxicity, leads to poor quality of life, and reduces patient survival.

Why malnutrition occurs in cancer patients?

Malignancy per se or treatment of the malignancy (such as chemotherapy, radiotherapy, or surgical treatment) can lead to loss of test, decreased appetite, nausea, vomiting or diarrhea, oral lesions, severe mucositis, and GI complications such as dysphagia, ileus, intestinal obstruction, malabsorption, short bowel syndrome, and fistulae, which can lead to malnutrition [28].

Nutritional support reduces symptoms, improves the quality of life, reduces weight loss, prevents catabolism, and improves outcomes in cancer patients.

Indications of PN [27, 29, 30]

- PN is not recommended routinely in well-nourished cancer patients because of the lack of advantages and associated harmful effects.
- Access to the digestive tract is not possible for a prolonged period due to GI complications such as perforation, intestinal obstruction, high-output entero-cutaneous fistulas, or chylothorax.
- Chemotherapy or radiotherapy-induced GI toxicity limiting oral/enteral intake for more than 1–2 weeks in cancer patients.
- As anticancer therapy is ineffective in rapidly progressive malignant diseases and terminal stages of malignancy, PN is unlikely to benefit such patients.
- In patients receiving hematopoietic stem cell transplantation, PN is recommended if oral/EN is limited due to severe mucositis, ileus, or intractable vomiting.

Nutritional requirements

The total daily energy expenditure is about 20–25 kcal/kg/day for bedridden cancer patients and 25–30 kcal/kg/day for ambulatory cancer patients [27, 29]. Recommended protein intake is >1 gm/kg/day and, preferably up to 1.5 gm/kg/day [27].

The proportion of carbohydrates and lipids is roughly 40–50% or less and up to 50% of non-protein energy requirements, respectively [31]. The requirement of lipids is about 0.5–1.5 gm/kg/day (up to a maximum of 2 gm/kg/d).

Higher fat to carbohydrate ratio to provide non-protein energy is recommended in weight-losing, cachectic cancer patients with insulin resistance because of the advantages of lipids, such as increased energy density and ability to reduce the glycemic load [27].

CARDIAC DISEASE

Patients with chronic heart failure (CHF) carry the risk of malnutrition due to decreased energy intake, increased energy expenditure and impaired anabolism, and high mortality in patients with CHF with cardiac cachexia [32]. Reduced bowel perfusion due to decreased cardiac function can cause edema of the bowel wall leading to malabsorption [32].

In cardiac patients, oral supplementation and enteral nutrition are preferred, and PN is needed in very few patients who cannot take adequate oral or enteral nutrition.

Because of the potential risk of volume overload and hyponatremia, PN should be used cautiously, preferably using concentrated PN solutions. Lipid emulsion can provide greater calories (9 kcal/gm) with a smaller volume.

CRITICAL ILLNESS

Critical illness refers to seriously ill medical or surgical conditions that need intensive care and is associated with a greater risk of infection, longer ICU stays, and higher mortality. Malnutrition is quite common in critical illness (occurs in about 38% to 78% of patients) and increases morbidity, mortality, and hospital-related cost [33]. Malnutrition in critical illness usually occurs due to multiple causes, such as increased energy expenditure, marked catabolism, decreased food intake for a prolonged period due to anorexia, and different medical or surgical gastrointestinal disorders.

In critical illness, adequate nutrition is important because malnutrition is associated with impaired clinical outcome, starvation or underfeeding leads to increased morbidity and mortality, and timely optimum nutrition decrease hospital stay and morbidity [34–36].

Metabolic changes: Depending on the duration of critical illness, it is divided into three stages: acute early phase, acute late phase, and post-acute late phase [11]. Different metabolic changes according to these stages help in planning the appropriate nutritional therapy considering varying needs. In the acute early phase, catabolism-induced increased endogenous generation of energy helps to meet the demand of the body in critically ill patients, and therefore, early use of PN with the provision of standard energy requirements is likely to cause overfeeding [37]. Characteristics of metabolism at the different time frames in critical illness as summarized in Table 56.2 [11].

Enteral nutrition vs. parenteral nutrition

In critically ill patients, EN is preferred and recommended over PN because of its safety and various advantages by all recent international guidelines [6, 11, 38]. In the CALORIES trial, PN is found to be as safe as EN in a critically ill patient when the dose of PN is hypocaloric, which is equivalent to EN dose [39]. So, the advantages of EN may be due to differences in the intake of calories rather than the route; therefore, using PN in an appropriate dose is as safe as EN [40].

When to provide nutrition in critical illness?

The timing of the initiation of PN is important and controversial critically ill patients. No benefit or harm was documented with early nutrition in the recent TARGET Trial (2018) [41, 42]. In the largest nutrition EPaNIC trial (2011), the potential harm with early PN and benefits such as enhanced recovery, fewer complications, and reduced healthcare costs were demonstrated with the late initiation PN [10]. So, in adequately nourished crit-

Table 56.2 Metabolic characteristic of critical illness

Stage	ICU days	Metabolism	Characteristic
Acute phase early period	1–2	Catabolism	Metabolic instability and severe increase in catabolism
Acute phase late period	3–7	Catabolism	Significant muscle wasting and stabilization of the metabolic disturbances
Post-acute late phase	After day 7	Anabolism	Improvement and rehabilitation
		Catabolism	Chronicity with persistent inflammatory/catabolic state and prolonged hospitalization.

ically ill patients with low nutrition risk, if PN is indicated, it should be administered late because of the harmful effects of early PN and the benefits of the late initiation PN. Recent European guidelines recommend initiation of PN between ICU days 3 and 7 (ESPEN 2019), while American guidelines recommend initiation of PN after 7 days (ASPEN/SCCM 2016) [6, 11].

Indications of PN

Adequate nutrition is beneficial during and after the ICU stay in critical illness. Therefore, in critically ill patients, exclusive or supplemental PN is indicated when oral/EN is contraindicated or fails to achieve nutritional targets, which prevents underfeeding associated risks and poor outcomes:

- Critically ill patients who are well-nourished and have a low risk for malnutrition generally do not need exclusive PN in the first seven days of an ICU stay [6, 43].
- In critical patients with high nutrition risk or severe malnutrition, initiate exclusive PN at the earliest following ICU admission if EN is not feasible [6].
- Supplemental PN: If oral/EN fails to meet >60% of energy and protein requirements after seven to ten days, the use of supplemental PN is recommended in patients with a low or high nutritional risk [6]. Supplemental PN is a step-up approach that helps to provide timely and optimal nutrition support during critical illness.

Nutritional requirements and management

How to initiate PN in critical illness?

Current literature is against the traditional practice of aggressive nutrition in the early stages of critical illness [44]. Both European and American guidelines recommend a strategy to provide hypocaloric PN (≤20 kcal/kg/d or 70–80% of estimated energy requirements) with an adequate protein supplementation (≥1.2 gm protein/kg/d) in the first week of hospitalization in the ICU to avoid overfeeding [6, 11]. The strategy to provide hypocaloric PN reduces peripheral insulin resistance and risk of hyperglycemia and improves glycemic control with resultant increases in the safety of PN. After the patient stabilizes, the dose of PN may be increased gradually to achieve 100% of the estimated energy requirements [6].

The nutritional requirements of critical and stable patients are summarized in Table 56.3 [6, 11, 12].

Energy expenditure: Indirect calorimetry is the preferred method to calculate caloric needs [6, 11]. The approximate total energy expenditure in critically ill patients is about 20 to 30 kcal/kg/day [12]. Initial administration of 70–80% of the measured energy expenditure is beneficial, whereas higher or lower energy intakes are both harmful [45–47]. Critical patients with low serum phosphorus levels (less than 0.65 mmol/L or 2 mg/dL) are prone to develop refeeding syndrome. So in such patients, restrict calorie intake to 50% of the calculated energy needs for 2 to 3 days to prevent the refeeding syndrome [48].

Protein requirements: In the acute phase of critical illness, increased catabolism causes loss of protein and muscle wasting [49, 50], and therefore requirements of protein increase considerably with illness severity. Inadequate protein supplementation may be harmful, and supplementation of protein intake may be beneficial and found to reduce the mortality in critically ill patients in recent literature [45, 51–53].

Table 56.3 Nutritional requirements in critical and stable patients

	Critically ill patients	Stable patients
Total calories	20 to 30 kcal/kg/d	20 to 30 kcal/kg/d
Protein	1.3 (1.2–2.0) gm/kg/d	0.8 to 1.5 gm/kg/d
Carbohydrate	Not >5 mg/kg/min	4–5 mg/kg/min
Lipid	Less than 1.5 gm/kg/d (100 gm/wk)	1 gm/kg/d
Fluid	Minimum needed to deliver adequate macronutrients	30 to 40 mL/kg/d

As per current recommendations, a higher amount of protein should be provided to critically ill patients (i.e., up to 1.3 gm/kg/day as per ESPEN guidelines (2019) and 1.2–2.0 gm/kg/day as per ASPEN/SCCM guideline (2016) [6, 11]. Administration of protein in a low dose initially (<0.8 gm/kg/day before day 3) and subsequently gradually increasing its dose (>0.8 gm/kg/d after day 3) is beneficial and reduces mortality [54].

Combining exercise with calorie and protein supplementation is very important because it helps to maintain muscle mass and function, reduces protein catabolism, and improves outcomes [11, 55, 56].

Carbohydrate requirements: Carbohydrate is the preferred source of energy in the early phase of critically ill patients. The minimum amount of carbohydrate requirement recommended in ICU patients by 2003 ESPEN guidelines was 2 gm/kg of glucose per day [34] and 1–2 gm/kg/day by the German Association for Nutritional Medicine [57]. But in current literature, the lower limit is removed due to a lack of evidence, and 2019 ESPEN guidelines recommend that in ICU patients receiving PN, the amount of glucose should not exceed 5 mg/kg/min [11].

Avoid Hyperglycemia in critically ill patients because it is harmful and is associated with an increased risk of complications and higher mortality. In critically ill patients, the recommended target blood glucose ranges from 140 or 150 to 180 mg/dL [6, 58]. The use of insulin infusion is recommended for achieving normoglycaemia because controlling blood sugar decreases mortality in critically ill patients. Insulin infusion is used when blood glucose is >150 mg/dL to maintain it below 180 mg/dL [59].

Lipid emulsions: For critically ill patients who are hemodynamically stable, lipid emulsion is an essential part of PN, as it provides a dense source of non-protein calories and essential fatty acids [11].

Requirements: Administration of intravenous lipid emulsions can be initiated safely at a rate of 0.7 gm/kg/day, and the total dose of lipid should not exceed 1.5 gm lipids/kg/day or a maximum of 100 gm/week and should generally provide about 30% of total calories [6, 11, 60, 61].

Selection of lipid emulsions: Lipid emulsions containing soybean oil are the mainstay and the first-generation lipids for parenteral nutrition. Alternative lipid emulsions, such as Generation 2 (combining soybean oil with medium-chain triglycerides), Generation 3 (using olive oil), and Generation 4 (using fish oil) lipid emulsions, have been developed to decrease the harmful effects of the omega-6-rich linoleic acid content and to lower the ratio of omega-6 to omega-3 fatty acids [62]. Because of the potential risks associated with the use of pure soybean oil emulsions in critically ill patients, 2016 SCCM/ASPEN guidelines recommend against its use during the first week of starting PN [6]. On the contrary, omega-3 fatty acid enriched fish oil containing PN is beneficial and reduces the risk of infection and sepsis, and shortens the length of stay in both ICU and hospital [63].

So current literature recommends the use of fish-oil containing lipid emulsions as part of PN in surgical and high-risk critically ill adult patients (e.g., sepsis, acute respiratory distress syndrome (ARDS), persistent inflammation catabolism syndrome [PICS]), although evidence to support its use in non-surgical patients is not sufficient [6, 11, 64, 65]. Because of clinical benefits over the standard lipid emulsions, provide 0.1–0.2 gm/kg/day fish oil containing lipid emulsions [rich in EPA (eicosapentaenoic acid) + DHA (docosahexaenoic acid)] in patients receiving PN [11].

Monitoring: While administering lipid emulsions, measure serum triglyceride concentrations at baseline, monitor it regularly, and adjust the dose of lipid emulsions to maintain triglyceride levels below 400 mg/dL (4.5 mmol/L) [64].

Micronutrients and glutamine

Vitamins and trace elements (micronutrients) are essential components of PN. As commercially available PN formulations do not contain vitamins and trace elements, their separate administration is needed. In addition, a high dose of micronutrients may improve the outcomes of critically ill patients [66].

Parenteral glutamine supplementation is not recommended in critically ill, unstable, and complex ICU patients and patients with multi-organ failure, especially with liver and renal failure in recent guidelines (Canadian guidelines 2015, ASPEN guidelines 2016, ESPEN guideline 2019) [6, 11, 67].

GASTROINTESTINAL FISTULAE

Gastrointestinal (GI) fistulas divert intestinal contents, most commonly to the skin (cutaneous, gastrointestinal fistula). Common causes of GI fistula are crohn's disease, injury to the bowel, bowel surgery, radiation injury, abscess, and foreign body penetration.

High output GI fistulas (loss greater than 500 ml of fluid in 24 hours) might cause massive loss of fluid, electrolytes, proteins, vitamins, and trace minerals resulting in complications like severe dehydration, fluid, electrolytes, acid-base abnormalities, and malnutrition (which occurs in about 55–90% of patients) [68, 69]. In addition to these abnormalities, profound nutrient depletion and sepsis are leading causes of death in patients with high-output GI fistulas [70].

Nutritional support

The provision of optimum nutrition is necessary because it significantly improves clinical outcomes by accelerating the spontaneous healing rate, enhancing the closer of the fistula, and reducing the mortality rate in patients with high-output GI fistulas [71, 72]. Therefore, PN is started in patients with high output fistula after initial fluids and electrolytes resuscitation and control of sepsis.

Indication: PN has a supportive role, and its indications in patients with GI fistula are [71, 73, 74]:

- High-output fistula (e.g., >500 mL/day), presence of distal intestinal obstruction, or length of intestinal before the fistula less than 75 cm because these patients cannot tolerate oral or EN.
- When oral or EN fails to provide adequate nutrition beyond 7 days.

- Supplemental PN is provided when EN alone cannot achieve the nutritional goal to meet their metabolic needs.

PN improves nutritional status by providing adequate nutrition, allows time to correct sepsis and thereby prepare them for reconstructive surgery, and helps to postpone extremely hazardous emergency surgical intervention in severely ill patients with GI fistulas.

Nutritional requirements and management: Patients with high-output fistula requires 25 to 35 kcal/kg per day of total caloric intake and 1.5–2.0 gm/kg/d of protein [75]. As protein loss in the effluent of high output fistula can be as high as 75 gm/day, ASPEN-FELANPE clinical guidelines recommend more protein (up to 2.5 gm/kg/d) supplementation in adult patients with high output fistula [73].

Lipids are usually given roughly 20–30% of calories. The use of lipid emulsion containing omega-3 fatty acid-enriched fish oil in PN is beneficial because it is a calorically dense nutrient and has an immune-enhancing effect that reduces the risk of sepsis and shortens the duration of hospitalization [63].

Vitamins and trace elements deficiency is common in malnourished patients, and its supplementation is recommended. The recommended vitamin C and zinc dose is about ten times the daily allowance, while the dose of other vitamins is two times normal [76].

INFLAMMATORY BOWEL DISEASE (IBD)

Inflammatory bowel diseases are chronic, relapsing, and debilitating inflammatory disorders of the gastrointestinal tract, and their most common causes are crohn's disease (CD) and ulcerative colitis (UC).

Malnutrition occurs in about 6% to 16% of patients with IBD [77, 78].

The etiology of malnutrition in IBD is multifactorial, results from decreased food intake, poor digestion, malabsorption, increased losses of nutrients, increased energy requirements, a short length of the intestine due to resection, and drug or surgery-related factors [79, 80].

Adequate correction of malnutrition is essential in patients with IBD because it worsens the prognosis and adversely affects the quality of life by increasing complication rates and mortality [81, 82].

PN does not increase the remission rate or decrease the need for surgery in patients with IBD. Therefore, PN and bowel rest should not be used routinely as primary therapies for IBD. PN is less effective than steroid therapy in the treatment of CD. Correction of dehydration and replacement of various micronutrients are more critical than bowel rest alone.

Indications of PN

- EN is preferred over the PN, and PN is indicated only in selected patients with IBD [81–84].
- If oral or EN is insufficient to deliver nutrition targets (cannot supply >60% of energy needs) in patients with crohn's disease due to GI tract dysfunction or short bowel.
- If oral or EN is not possible due to severe vomiting or diarrhea and absence of access.
- If oral or EN is contraindicated due to paralytic ileus, an obstructed bowel, intestinal ischemia, or severe shock.
- If the patient develops complications such as an anastomotic leak or a high output intestinal fistula.
- In the perioperative period, provide PN if oral or EN cannot be initiated within 7 days.
- In the postoperative period, provide PN if oral or EN cannot be initiated within 7 days.

LIVER DISEASE

The liver is labeled a "workhorse" because it performs multiple complex tasks such as metabolism, alteration, synthesis, storage of various nutrients, and detoxifying different toxic substances.

Malnutrition is commonly seen in patients with liver disease, and its prevalence is about 20% in compensated cirrhosis and as high as 50%–90% in advanced cirrhosis [85, 86].

Important causes of malnutrition are excessive use of alcohol, decreased food intake, impaired gastric emptying, impaired digestion, malabsorption, altered metabolism, increased resting energy expenditure, insufficient nutrient storage and synthesis, and abnormal nutrient losses [86, 87].

Early detection of malnutrition in liver disease is important because it adversely affects outcomes by causing loss of muscle mass (sarcopenia), increased rate of complications (encephalopathy, variceal bleeding, and infection), a longer stay in the hospital, and higher mortality [88–91]. Early diagnosis and proper treatment of malnutrition, ascites, and hyponatremia can reduce morbidity and mortality in patients with liver disease.

Indications of PN

Selective use of PN is beneficial in patients with hepatic failure as it reduces complication rates, duration of mechanical ventilation, and stay in ICU [92].

Common indications of PN are [92–95]:

- When oral or EN are inadequate or contraindicated, PN is used as second-line treatment according to the current recommendation for non-cirrhotic patients.
- PN is beneficial in patients with poor oral intake for a prolonged period and problems like hepatic encephalopathy, gastrointestinal bleeding, and impaired gut motility or ileus.
- In patients with moderate or severe malnutrition, prompt administration of PN is recommended, as in other critically ill patients.
- To provide early postoperative nutrition after liver transplantation and surgery when oral nutrition or EN is not feasible. Postoperative PN helps to reduce rates of complication, length of mechanical ventilation, and ICU stay.
- Considered PN in the presence of problems like unprotected airways, compromised cough and swallow reflexes, and hepatic encephalopathy.

Nutritional requirements and management

Nutritional requirements in patients with liver diseases vary depending upon the type of liver disease, the severity of illness, malnutrition, and associated complications.

Energy requirements

Energy expenditure usually increases in patients with acute liver failure, alcoholic steatohepatitis, and cirrhosis, but it is normal in non-alcoholic fatty liver disease (NAFLD). The basal metabolic rate should be calculated using the actual body weight for patients with cirrhosis of the liver without ascites, but for patients with cirrhosis of the liver with ascites, use the ideal body weight for the calculation [6, 94].

Energy requirements increase in cirrhotic patients with acute complications, refractory ascites, malnutrition, or hepatic encephalopathy, but not for overweight or obese patients (as summarized in Table 56.4) [6, 92, 94, 96, 97].

In cirrhotic patients, carbohydrates should provide 50–60%, and lipids should provide about 40–50% of non-protein energy requirements [93].

Protein requirements

Providing optimum protein supplementation to the cirrhotic patient is the most important and challenging part of nutrition. Protein restriction to prevent the development of hepatic encephalopathy (HE) is one of the most common misconceptions. Restriction of protein should be avoided because it increases protein catabolism, and on the contrary, high protein supplement actually improves mental status and does not precipitate or worsen HE [98–100].

The requirement for protein increases in malnourished and/or sarcopenic cirrhotic patients, patients requiring frequent or large-volume paracentesis, and obese cirrhotic patients for preserving lean body mass, as summarized in Table 56.5 [6, 92, 94].

Vitamins and micronutrients

Vitamins and micronutrient deficiencies are frequently seen in patients with liver diseases, especially those with alcoholic cirrhosis. Such patients require the supplementation of vitamins (both fat and water-soluble) and micronutrients. In addition, increased prothrombin time (PT) is frequently encountered in patients with liver diseases, and vitamin K is routinely supplemented to correct PT; however, evidence regarding its efficacy is limited [101, 102].

Zinc deficit is common in patients with cirrhosis of the liver, and evidence of the benefits of zinc supplementation in hepatic encephalopathy is growing [103–107].

Fluid and salt requirements

Cirrhosis affects the patient’s ability to handle salt and water and may cause ascites and dilutional hyponatremia. Ascites is the common complication of cirrhosis of the liver, and in patients with severe anasarca and ascites, salt and water restriction may be necessary. Hyponatremia is prevalent in patients with ascites due to cirrhosis and is associated with higher morbidity and mortality [108].

Salt restriction: Dietary sodium restriction is the first-line therapy in ascites, and recent guidelines recommend intake of about 80–113 mEq sodium or 5–6.5 gm of salt per day [92, 109]. While prescribing a low-salt, unpalatable diet, it is essential to consider the trade-off between reducing caloric intake, which can lead to a risk of malnutrition from decreased food intake, and its moderate advantage in reducing ascites [94, 110]. Therefore, salt restriction is not recommended in patients with cirrhosis in the absence of ascites.

Fluid restriction: Restriction of fluid to 1 to 1.5 L per day should be considered only in patients with clinical hypervolemia with severe hyponatremia (serum sodium <125 mmol/L) [109]. Fluid restriction

Table 56.4 Energy requirements in liver diseases

Requirements	Clinical conditions
25–30 kcal/kg/d	Compensated liver cirrhosis
30–35 kcal/kg/d	Acute liver failure, alcoholic hepatitis, decompensated cirrhosis (in nonobese individuals), cirrhotic with malnutrition, hepatic encephalopathy, preoperatively and postoperative cirrhotic patients
25 kcal/kg/d	Obese cirrhotic patient
35–40 kcal/kg/d	Critically ill cirrhotic patients

Table 56.5 Protein requirements in liver diseases

Requirements	Clinical conditions
1.2 gm/kg/d	Non-malnourished compensated liver cirrhosis
1.5 gm/kg/d	Decompensated cirrhosis (in nonobese individuals), malnourished and/or sarcopenic cirrhotic patients
1.2–1.5 gm/kg/d	Preoperatively and postoperative cirrhotic patients, hepatic encephalopathy
1.5–2 gm/kg/d	High volume recurrent ascites with sarcopenia
2.0–2.5 gm/kg/d	Obese cirrhotic patient
>1.2 gm/kg/d	Critically ill cirrhotic patients

is not recommended in hypovolemic hyponatremia and mild to moderate hyponatremia.

PANCREATITIS

Nutritional considerations

Acute pancreatitis (AP) is severe in about 20% of patients, and severe acute pancreatitis increases the mortality rate by 19–30% [111]. Severe acute pancreatitis is a hypercatabolism state leading to sustained protein catabolism and increased energy requirements with resultant nutritional risk [112]. Timely adequate nutrition plays a key role in the management of severe acute pancreatitis.

The concept of "Pancreatic Rest" is changing: Formerly, in the early stages of severe acute pancreatitis, patients were kept nil by mouth and given PN to provide rest to the pancreas. The previously popular concept of "Pancreatic Rest" was based on the presumption that oral or enteral feeding could stimulate pancreatic enzyme secretion, causing autodigestion of the pancreas and surrounding tissues and worsening pancreatitis.

The rationale for discarding "Pancreatic Rest" and changing to EN in the early phases of severe acute pancreatitis are:

- The lack of oral or enteral nutrition leads to a loss of intestinal mucosal barrier function and increased bacterial translocation, resulting in an increased risk of complications such as pancreatic infection and necrosis [113].
- During acute pancreatitis, the secretion of pancreatic enzymes decreases significantly, with the most severe cases having the lowest secretion. As a result, even if EN is taken, it does not increase secretion because it is already reduced, making EN not harmful in severe acute pancreatitis [114, 115].
- The beneficial effects of oral/EN are improvement in nutritional status, stimulation of intestinal motility, increase in splanchnic blood flow, and maintenance of gut integrity which inhibits bacterial translocation, reduction of pancreatic infection, decrease in local and systemic inflammation risk, and reduced mortality [116–118].
- Use of parenteral nutrition for bowel rest has a potential risk for hyperglycemia, electrolyte imbalances, catheter-related infections, and sepsis, and is more expensive than EN [119, 120].

To conclude, the concept of "Pancreatic Rest" is outdated, detrimental, and should be abandoned [117, 121–123].

Enteral vs. parenteral nutrition

In the early phases of severe acute pancreatitis, EN is safer, more effective, and is preferred compared with parenteral nutrition according to different studies [124–128], current reviews [113, 116–118], and recent guidelines [6, 112, 123, 129–133].

Compared to PN, oral or EN has demonstrated multiple benefits such as decreased infectious complications, risk of complications, mean length of hospital stay, rate of multiple organ failure, and mortality rate in patients of severe acute pancreatitis in several studies [124–128, 134, 135].

Timing of initiation of EN: The early EN (i.e., initiated within 72 hours [112, 132, 136], 48 hours [6, 125, 130, 135, 137–141], or 24 hours [123, 142, 143] had significant benefits over the delayed EN such as decrease complication rate, organ failure, mortality, length of stay in the hospital, and cost-effectiveness.

It is very important to start EN early in moderate to severe acute pancreatitis because the inability to provide EN for >72–96 hours carries the risk of the rapid deterioration of nutrition status and resultant complications such as increased mortality, frequency of infected necrosis, and length of stay in hospital [6, 138].

Route of nutritional support: The most effective route of nutritional support in acute pancreatitis is determined based on the severity of diseases, associated local and systemic complications, and nutritional status at the time of admission.

Oral feeding: Patients with mild acute pancreatitis should consume normal food intake as tolerated, and the use of EN or PN is not recommended [6]. Recent guidelines [AGA (2018), NICE (2018), and ESPEN (2020)] recommend early initiation of oral feeding in patients with mild acute pancreatitis instead of traditional 'nil-by-mouth' or delayed oral feeding (initiation after reduction of serum amylase and lipase levels, resolution of abdominal pain and bowel sounds become normal) [112, 123, 132].

Early oral feeding (within 24 hours) is safe, and well-tolerated, with no differences in adverse events compared to standard oral refeeding or EN, may shorten the length of hospital stay as well as costs, and help in rapid clinical improvement [144–147]. Oral feeding is usually started when abdominal pain, nausea, and vomiting decreases, the patient feels hungry and intestinal obstruction or ileus are excluded (it is not necessary to wait until abdominal pain resolves completely or serum lipase concentrations decline) [112, 122, 129, 148, 149]. If the patient is unable to take oral intake within 72 hours, EN should be initiated on day 4 [145].

Enteral nutrition (EN): EN is a cheaper, safer, and the most preferred modality for nutritional support in severe acute pancreatitis, where feeding is provided directly into the stomach via a nasogastric tube (NG) or post-pyloric region by a nasojejunal tube (NJ) [128]. If a patient with acute pancreatitis is unable to eat, providing nutrition by enteral feeding is beneficial and preferred over parenteral nutrition.

It is important to remember that enteral feeding can be administered safely and successfully even in the presence of complications such as pseudocysts, ascites, and/or fistulas [150, 151].

In severe acute pancreatitis with high intraabdominal pressure (IAP) and abdominal compartment syndrome having abdominal distension, paralytic ileus, and high gastric residual volume, EN may be initiated cautiously by using nasojejunal as a preferred route [112, 131]. Monitor the intraabdominal pressure and the clinical condition continuously and closely in such patients. EN is initiated gently at a 10–20 mL/h rate via the nasojejunal route when intraabdominal pressure (IAP) is <15 mmHg, but IAP >15 mmHg may need temporary reduction or discontinuation of EN due to higher rates of feeding intolerance [112, 131, 152].

Because of physiological benefits, at least a small amount of EN may be administered supplementary to PN in patients with severe AP and open abdomen, if feasible [112].

Gastric vs. jejunal nutrition

Nasogastric feeding is a preferred route for EN because it is simpler, cheaper, easier to insert, requires less time to start nutrition, can provide adequate nutrition effectively, is safe in patients with low risk of aspiration, and as compared to the nasojejunal route of feeding carries a similar risk of exacerbation of pain, tolerance to EN, infectious complications, mortality, and length of hospital stay [112, 129, 153–161].

Nasojejunal feeding is preferred for EN in patients with a high risk of aspiration, who cannot tolerate gastric feeding, severe gastroparesis, partial gastric outlet obstruction due to pancreatic edema or pseudocysts, and in patients who have undergone minimally invasive necrosectomy [112, 117, 136, 162].

Mild acute pancreatitis: About 80% of acute pancreatitis patients experience a mild form of the disease that resolves on its own, allowing them to consume solid food without requiring nutritional support, such as EN or PN [6, 112]. In mild acute pancreatitis, starting with a soft low-fat solid diet is safe, effective (as it does not worsen abdominal pain, provides more calories than a clear liquid diet, and results in shorter hospital stays), and well-tolerated [146, 163–167]. Therefore, the traditional practice of initially providing a liquid diet and advancing to a solid oral diet is not recommended in mild acute pancreatitis.

Indications of PN

Routine use of PN is unnecessary, as PN is now known to be more expensive, riskier, and no more effective than EN in patients with acute pancreatitis. PN should not be initiated until all attempts are made with EN for at least 2–3 days. In acute pancreatitis, PN is indicated in selected patients [6, 112, 129, 133, 168, 169]:

- If EN is not possible or contraindications (e.g., prolonged paralytic ileus, duodenal obstruction from pancreatic edema or pseudocyst, complex pancreatic fistulae, hemodynamic instability, and the need for inotrope support).
- Unable to achieve targeted nutritional demand through EN.
- When enteral access cannot be maintained, or the patient cannot tolerate a nasal tube due to nasal irritation.
- If enteral feeding leads to exacerbation of abdominal pain and therefore, patients are unable to tolerate EN.
- In abdominal compartment syndrome with IAP >20 mmHg, patients cannot tolerate EN, and PN is indicated.

When tolerance to EN increases with recovery, the volume of PN should be decreased gradually, and PN should be transitioned to EN as soon as possible.

Nutritional requirements and management

Severe acute pancreatitis is characterized by substantial protein catabolism, so protein requirements are higher than in healthy individuals. Therefore, when PN is administered, a mixed source of energy from carbohydrates, fat, and protein should be preferred, and particular attention should be given to avoiding overfeeding and hyperglycemia. Rough guidelines for nutritional requirements in severe acute pancreatitis are:

- Energy: 25–30 kcal/kg/day
- Protein: 1.2 to 1.5 gm/kg/day
- Carbohydrate: 4–6 gm/kg/day
- Lipid: up to 2 gm/kg/day

Carbohydrate supplementation: Hyperglycemia frequently occurs in patients with acute pancreatitis due to pancreatic endocrine dysfunction. Blood sugar should be monitored closely, and insulin treatment is recommended to treat hyperglycemia with a goal of keeping blood sugar less than 180 mg/dL (10 mmol/L).

Lipid infusion: As hypertriglyceridemia is an important cause of acute pancreatitis; lipids should be infused with proper monitoring of triglyceride levels. In the absence of severe hypertriglyceridemia (>350 mg/dL) or thrombocytopenia, IV lipids appear safe and effective, especially if glucose intolerance is present. The triglyceride level should be checked before initiating PN, monitored regularly, and kept below 400 mg/dL. When the triglyceride level exceeds 400 mg/dL (4.5 mmol/L), lipid infusion should be discontinued temporarily. To prevent hypertriglyceridemia, IV lipids should be administered gradually over a period of 10–12 hours.

Glutamine supplementation: The use of glutamine supplementation is beneficial and recommended in patients with severe acute pancreatitis receiving parenteral nutrition [112]. The advantages of glutamine are limited only to patients receiving parenteral nutrition, so do not supplement glutamine to patients of severe acute pancreatitis receiving enteral nutrition. The recommended dose of L-glutamine is 0.20 gm/kg per day, and glutamine supplementation in PN is found to reduce infectious complications and mortality [170, 171].

PERIOPERATIVE NUTRITION

Malnutrition in hospitalized patients is very common, with about 20% and 40% incidence [172]. Many major surgical diseases (e.g., malignancy, inflammation, gastrointestinal dysfunction, and burns) result in malnutrition, causing catabolic effects leading to inflammatory responses, protein catabolism, and nitrogen losses. Gastrointestinal surgery-related causes of malnutrition are pre-existing chronic disease, anorexia, prolonged ileus, pre and postoperative fasting, malabsorption syndrome, intestinal obstruction, and previous surgical bowel resection [173]. Compared with well-nourished patients, malnutrition in surgical patients is associated with detrimental effects like longer hospital stays, increased hospital costs, and increased postoperative morbidity and mortality (increased susceptibility to infection, poor wound healing, and risk for death after surgery) [174–176].

The decision to use PN in surgical patients depends on the state of health before surgery, the severity of malnutrition, whether the surgery is emergency or elective, the type of surgical procedure, the expected duration for return of normal gastrointestinal function, and how much energy and nutrient requirements patient can tolerate by oral or EN route postoperatively. PN is lifesaving in patients with prolonged gastrointestinal failure. Perioperative nutritional support aims to provide adequate macronutrients and micronutrients to minimize the catabolism and aggravation of malnutrition, promote muscle, immune, and cognitive functions, and decreases infectious and non-infectious postoperative complication rates with resultant fast postoperative recovery [177, 178].

Preoperative parenteral nutrition

Preoperative PN is indicated in severely malnourished patients (weight loss >10–15%, serum albumin <3.0 gm/dL, body mass index (BMI) <18.5 or nutrition risk index (NRI) score <83.5) who cannot achieve adequate nutrition orally or enterally [179, 180]. Preoperative PN aims to provide adequate energy, protein, micronutrients and restore glycogen stores [181].

Preoperative PN for 7–10 days in severely malnourished patients reduces the rate of postoperative complications and improves outcome, provided the operation can be safely postponed [180, 181, 182]. Restoration of the nutritional and metabolic status usually takes about 7 to 14 days, and PN is continued in the postoperative period. In patients with mild to moderate malnutrition, surgery need not be delayed for preoperative PN or EN, and avoid preoperative PN in such patients.

Postoperative parenteral nutrition

Postoperative parenteral nutrition should not be used routinely because of the increased risk of postoperative complications [182, 183].

Indications of postoperative nutritional support

Postoperative PN is indicated in the following conditions [6, 179, 180, 184–186]:

- Previously well-nourished patients are unlikely to resume oral and enteral feeds within 10 days due to postoperative complications impairing gastrointestinal function and preventing normal oral feeding, such as intestinal obstruction. But in well-nourished patients with a delayed return of gut function likely to resume oral intake or EN within 7 days, PN is not indicated.
- Previously malnourished patients in whom oral intake or EN is not feasible or not tolerated within 5–7 days.
- In previously severely malnourished patients undergoing emergency surgery, initiate PN as soon as possible.
- Supplemental PN: Combining EN and PN should be considered for patients who require nutritional support but cannot meet at least 50% of their energy and nutrient needs via oral or enteral intake for more than seven days.

Timing of initiating PN in postoperative patients

The optimal timing of initiation of PN is determined based on the patient's clinical condition and preoperative nutritional status [6, 179, 180, 185].

- Immediate postoperative PN support (started on PO day 1) may be appropriate in patients as a continuation of preoperative nutritional support for severe malnutrition.
- Initiate PN as soon as possible in patients with severe malnutrition if oral intake or EN is unlikely.
- For patients who are nutritionally at risk and oral intake or EN is not possible, initiating PN within 3 to 5 days may be appropriate.
- In the absence of preoperative malnutrition, PN should be delayed for around 5 days after surgery as early PN does not provide any benefit in most non-critically ill patients [39, 187].
- Initiate supplemental PN after 7 days if oral and enteral intake alone cannot

achieve 50% or more of estimated energy and nutrient requirements in well-nourished, stable adult patients.

Common disorders for which postoperative PN is indicated include gastrointestinal anastomotic failure, gastrointestinal fistulas, postoperative mechanical bowel obstruction, diffuse peritonitis, paralytic ileus, severe acute pancreatitis, bowel ischemia, short bowel syndrome, etc.

In patients receiving PN postoperatively, supplement vitamins and trace elements with PN [177].

PULMONARY DISEASES

Nutritional considerations

There is a strong association between malnutrition and lung function. In chronic obstructive pulmonary disease (COPD), malnutrition is common (occurs in about 10% to 60% of patients) [188, 189] and is associated with higher morbidity, mortality rate, and healthcare costs [190–193].

The important causes of malnutrition in patients with COPD are decreased food intake, increased energy expenditure, depression, social isolation, aging, inflammation, and the use of medication such as corticosteroids [194].

- Effect of malnutrition on lung function: When calorie intake is inadequate in critically ill patients with pulmonary disorders, protein is catabolized to provide energy. When protein is used as a source of calories, it leads to catabolic muscle wasting. So, malnutrition can lead to reduced muscle strength and impairment of respiratory muscle function, which can decrease ventilatory drive and decreased response to hypoxia due to progressive diaphragmatic weakness with resultant precipitation or aggravation of respiratory failure [193, 195, 196]. Malnutrition-induced muscle weakness also adversely affects weaning from mechanical ventilators [197]. Moreover, malnutrition also alters pulmonary defense mechanisms and increases susceptibility to infection [198].
- Effect of pulmonary diseases on nutritional status: In advanced pulmonary diseases, a combination of, (a) Higher energy requirements due to increased work of breathing and systemic inflammation, and (b) Poor food intake lead to catabolism and resultant malnutrition and weight loss [199]. Underweight patients with the chronic pulmonary disease have a significantly increased risk of all-cause mortality [200].
- Effect of nutritional support on lung function: Nutritional support in COPD patients has shown modest improvement in various parameters such as respiratory (inspiratory and expiratory muscle strength) and non-respiratory (handgrip and quadriceps) muscle strength, respiratory muscle function, exercise tolerance, and quality of life and these benefits are greater in malnourished patients [201–205].

Nutritional requirements

Administration of nutrition by oral or enteral route is preferred. But if the gastrointestinal function is Administration of nutrition by oral or enteral route is preferred. But if the gastrointestinal function is impaired for a prolonged period, and adequate oral or EN is not feasible, PN is indicated. Patients with ARDS, COPD, respiratory failure and patients on mechanical ventilators need special consideration for their nutritional requirements. The nutritional needs of COPD patients vary and are determined by their clinical state (stable or exacerbation) and disease severity (ranging from mild to very severe) [206]:

- In COPD, requirements of Energy and protein are higher in moderately or severely malnourished patients, acutely unwell patients with infection, and patients who exercise to increase muscle mass [193].
- The recommended energy intake for patients with COPD is about 30 kcal/kg/day for weight maintenance [207] and may be as high as 45 kcal/kg/day for patients aiming to achieve weight gain [208]. In malnourished patients, energy requirements may be as high as 1.7 of resting energy expenditure (REE) [209].
- The recommended daily protein requirement varies based on clinical status, as summarized in Table 56.6 [193].
- Avoid overfeeding: Excess supplementation of dextrose and lipids is harmful. Administration of total energy that exceeds energy requirements increases CO_2 production and the work of breathing, which may be detrimental in patients vulnerable to the retention of CO_2.
- Lipids in stable patients: In respiratory disorders, the use of lipids is suggested because it provides more energy with less production of CO_2 and therefore reduces the work of breathing. So in spontaneously ventilated patients with COPD, the use of a higher amount of lipids (up to about 50%) and lesser carbohydrates (about 30%) is preferred [210]. While administering lipid emulsion as a part of PN, selecting lipid preparation containing omega-3 fatty acids-rich fish-oil is beneficial due to its anti-inflammatory action in high-risk, critical patients with ARDS [64, 211].
- Lipids in patients on a ventilator: It is recommended to use a low carbohydrate formula, which contains more lipids and less carbohydrates, for patients on a ventilator as it may shorten the duration of mechanical ventilation [212–214]. However, several studies failed to demonstrate the reduction in the duration of ventilatory support [215, 216], and recent ASPEN-SCCM Clinical Guidelines (2016) recommend against the use of high-fat/low-carbohydrate formulations to manipulate the respiratory quotient and reduce CO_2 production in acute respiratory failure patients in ICU [6].
- As patients with acute respiratory failure are susceptible to fluid accumulation, a concentrated nutritional formula that restricts fluid volume is recommended [6].
- Avoid hypokalemia, hypophosphatemia, hypocalcemia, and hypomagnesemia because they can adversely affect the strength of respiratory muscles. To avoid these abnormalities caused by refeeding syndrome, it is important to gradually initiate PN in severely malnourished patients with respiratory disorders.
- Vitamin D deficiency is common in patients with COPD [217–219]. The low value of vitamin D carries the risk of recurrent pulmonary infections [220], worsening lung function [221], and faster decline in lung function [222].

Vitamin D supplementation substantially reduced the risk of respiratory tract infections [223] as well as the exacerbation rates of COPD [224, 225].

So, GOLD guidelines 2020 recommends screening all COPD patients hospitalized for exacerbations to detect vitamin D deficiency and supplement vitamin D if necessary [206].

Table 56.6 Protein requirement in COPD patients

Requirements	Clinical state
0.8–1.5 gm/kg/d	Stable, non-malnourished COPD patients without nutritional risk
Up to 1.5 gm/kg/d	In acutely unwell (exacerbating) COPD patients, for daily requirements and avoid further protein losses For pulmonary rehabilitation, with exercise to gain or retain lean muscle mass Malnourished outpatients to achieve weight gain

SHORT BOWEL SYNDROME

Short bowel syndrome (SBS), also known as a small gut syndrome, is a relatively uncommon condition characterized by malabsorption which occurs most commonly due to extensive surgical resection of the small intestine.

Because of the short length of the remaining intestine, the area available for absorption reduces with the resultant malabsorption of macronutrients and/or water and electrolytes, causing diarrhea, dehydration, electrolyte imbalances, and malnutrition. These symptoms are severe if: (1) More than 75% of the small bowel is resected, (2) The terminal ileum and ileocaecal valve are removed, or (3) The remaining bowel is diseased with impaired absorption [226]. After massive intestinal resection, an intact colon, if in continuity, is vital in supporting the remaining small intestine in digestion and thereby reduces the dependency on PN [227–229].

The common causes of short bowel syndrome in adults are re-surgery performed for complications, mesenteric infarction, malignancy and radiation, surgical resection for crohn's disease, intestinal trauma, mesenteric vascular occlusion, and volvulus [230, 231].

Pathophysiology and presentations

- Severe diarrhea, electrolyte disturbances, and malnutrition: Loss of intestinal absorptive surface area, rapid transit time, and/or dysfunction of the remaining bowel reduces intestinal absorption leading to:
  - Large volume diarrhea, hypovolemia, metabolic acidosis, hypokalemia, hypomagnesemia, and hypocalcemia.
  - Malnutrition, weight loss, and deficit of water and fat-soluble vitamins.
- Gastric acid hypersecretion: Production of gastric acid secretion inhibitory hormones (normally secreted in the jejunum and distal ileum) reduces after the massive intestinal loss. Due to the loss of inhibitory hormones, gastrin levels increase, stimulating gastric acid secretion [232, 233].
- D-lactic acidosis: Bacterial fermentation of malabsorbed carbohydrates in the colon produces a substantial amount of D-lactic acid, which can lead to high anion gap metabolic acidosis [234].
- Nephrolithiasis: Due to multiple factors, the risk of calcium oxalate nephrolithiasis is high in patients with SBS [235, 236]. Normally oxalate in the diet combines with intraluminal calcium and is excreted in stool as insoluble calcium oxalate. In patients with SBS, large amounts of unabsorbed fat are available, and calcium preferentially binds with the same in the intact colon due to malabsorption. The resultant increased

unbound oxalate is absorbed freely and rapidly by the intact colon leading to hyperoxaluria, which predisposes patients to a higher risk of oxalate stone formation [237]. In patients with SBS, chronic dehydration, hypocitraturia, hypomagnesuria, low urine volume, and low pH increases the risk of developing kidney stones [235, 236]. In addition, in patients with SBS, multiple factors like chronic dehydration, hypocitraturia, hypomagnesuria, low urine volume, and low pH increases the risk of developing kidney stones [235, 238].

Nutritional management

Before the advent of PN, survival in acute SBS was very poor. The selection of nutritional treatment is based upon the severity of SBS and frequently needs home parenteral nutrition in severe cases. The need for nutrition requirement is variable in SBS, and it ranges from temporary support in the postoperative period to long-term supplementation depending on how much of the gastrointestinal tract is left, the site of resection, and the presence of the colon in continuity with the small bowel. Patients with SBS generally need PN when the length of the remaining functional small bowel is <50–70 cm with the presence of a colon in continuity or the length of the small bowel is <100–150 cm when the colon is absent [228, 239]. The metabolic and nutrient therapy of SBS is divided into 3 clinical stages:

1. First acute stage: The initial acute phase following resection usually lasts for three to four weeks and is characterized by large-volume diarrhea causing significant losses of fluid and electrolytes:

- In the initial acute phase of illness, patients need prompt administration of electrolytes containing intravenous fluids in large volumes to replace huge losses and correct fluid and electrolyte disturbances. The selection of IV fluid is based on existing electrolyte and acid-base disturbance, but supplementing balanced crystalloids or half normal saline with potassium is usually adequate.
- In critically ill unstable patients, patients should be kept NPO (nothing by mouth). Oral intake is not adequate in the majority of such patients at this stage and may carry the risk of aspiration and, therefore, can be harmful.
- PN is indicated if EN is not possible within one week in patients with severe SBS. PN is initiated only after correcting fluid and electrolyte disturbances and achieving hemodynamic stability. PN is the primary source of nutrition in the initial phase, but progression to EN is attempted when the bowel begins to adapt.
- Supplemental oral or EN helps to prevent mucosal atrophy and is essential to promote gut adaptation but administer combined feeding cautiously to avoid overfeeding [231]. EN in bolus form may cause diarrhea, so slow continuous overnight tube feeding is recommended in the initial acute phase, and it significantly increases the net absorption of lipids, proteins, and energy [240].

2. Second adaptive stage: Structural adaptation (hyperplasia with the resultant increase in absorptive surface area) and functional adaptation (slowed transit time to allow increased nutrient absorption) of the bowel may last for up to 2 years [231]:

- As enteral feeding is necessary for bowel adaptation in SBS, it should be started as soon as the volume of fecal loss decreases. The PN is reduced gradually, and oral or enteral intake is increased with caution to avoid excessive diarrhea and aim to provide adequate nutrition.

- In patients requiring PN, administration of a minimal 1 gm/kg/week of intravenous lipid emulsion is recommended to prevent essential fatty acid (EFA) deficiency [230].
- Overfeeding and the use of soybean-based lipid emulsions in patients receiving long-term PN increases the risk of intestinal failure-associated liver disease (IFALD) [241]. On the other hand, IV fish oil-containing lipid emulsions reduce the risk of IFALD in these patients [242–244].
- Administration of glutamine in either PN or EN is not recommended in SBS patients [230].
- As patients with SBS are at risk for fat-soluble vitamin deficiency, supplementation of vitamins A, D, E, and K is necessary [226].
- If the terminal ileum is resected or resection is greater than 100 cm of ileum, an injection of vitamin B12 should be given monthly [245].
- Hypomagnesemia is common because of the malabsorption of magnesium due to loss of the distal ileum, and its management consists of supplementation of magnesium and correction of sodium depletion [226, 246].

3. Third maintenance stage: In about 50% of adult patients, intestinal adaptation occurs significantly, and intestinal failure reverses completely within the first two years. No further improvement or adaptive changes occur in this stable phase, so long-term treatment is planned:

- The selection of treatment is based on the severity of SBS. Most patients with a severe type of SBS need home-based parenteral nutrition (HPN) for months to years or lifelong. Patients with adequate adaptation and absorption may not need PN.
- In patients with home-based PN, continuous PN infusion is avoided, and overnight cycle PN is recommended because it reduces the risk of intestinal failure associated liver disease (IFALD) [230], provides freedom from the infusion pump during the day, and maximizes the convenience of patients [247].
- Oral diet or EN is started using small volume and should be advanced slowly to small frequent meals [248].
- Patients with D-lactic acidosis need appropriate hydration, restriction of carbohydrate containing diet and administration of non-absorbable antibiotics against D-lactate forming bacteria, and thiamine supplementation.

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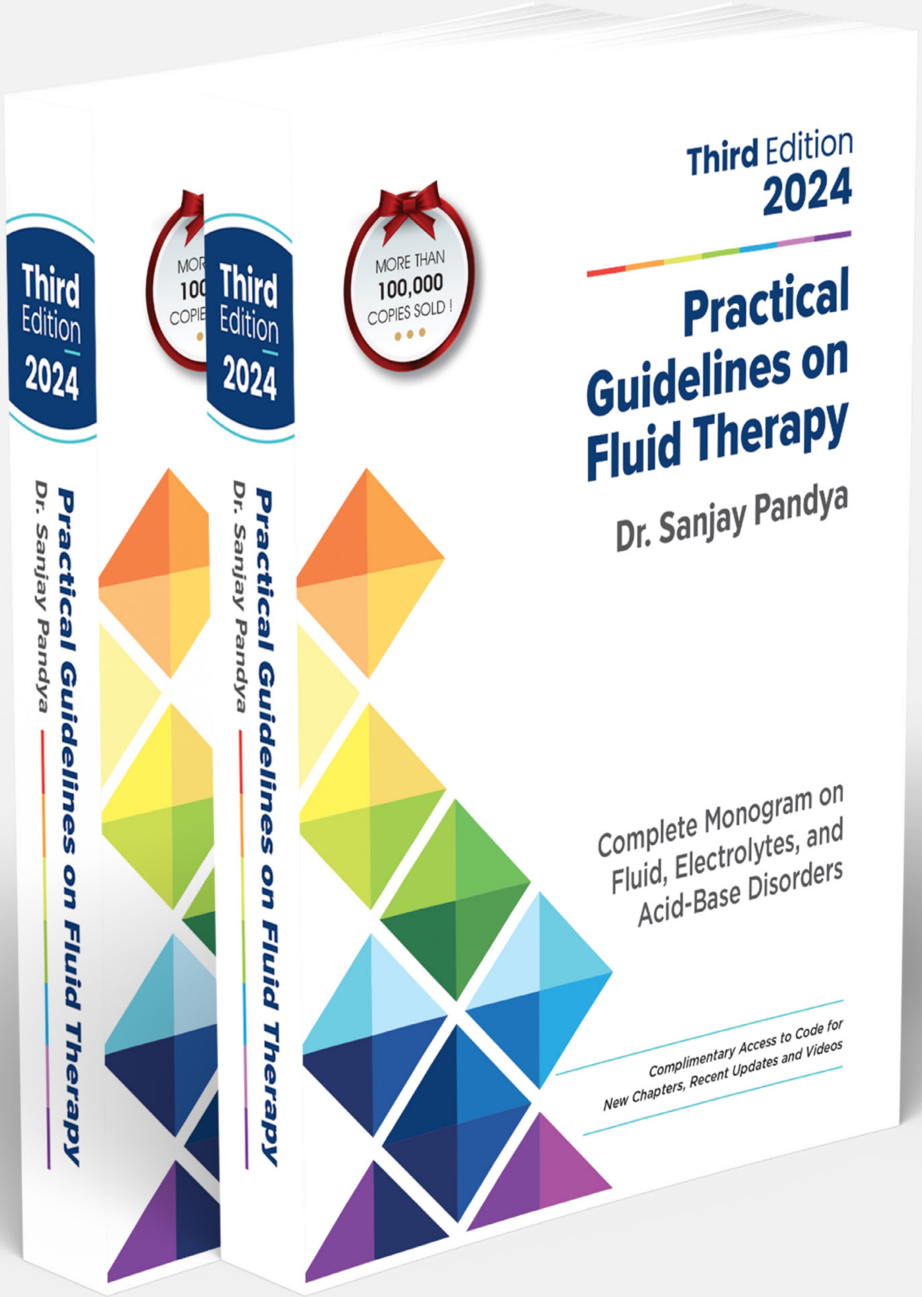
Chapter 57:

Parenteral Nutrition: Administration and Complications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57 Parenteral Nutrition: Administration and Complications

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ADMINISTRATION OF PARENTERAL NUTRITION

Parenteral nutrition (PN) is currently one of the most sophisticated forms of intravenous therapy. Appropriate use of parenteral nutrition provides life-saving treatment for patients who could not otherwise be nourished.

SELECTION OF MACRONUTRIENTS

Selecting an appropriate macronutrient mixture while administering parenteral nutrition in day-to-day practice is essential. Broad guidelines in the selection of the most suitable macronutrient solutions based on requirements for different patients are:

Indications of only dextrose containing crystalloids; avoid PN

In cases where patients are stable, not malnourished, and unable to consume oral intake for a brief period (less than a week), using PN support is unnecessary [1]. Instead, dextrose infusions (>100 gm/day in adults), electrolytes, and vitamins serve as the primary approach for short-term therapy in such individuals. Providing adequate dextrose (calculated as the daily energy requirement in kcal ÷ 3.4 = gm/day dextrose) fulfills calorie needs and helps conserve nitrogen [2].

Indications of amino acids plus dextrose-containing solutions, withhold lipid emulsion

Parenteral nutrition combining amino acids and dextrose may suffice to address nutritional needs over a short duration (less than one week) in patients who are stable and not malnourished, as long as their total caloric requirements remain relatively low. However, it is advisable to introduce lipid administration within ≤7 days of starting PN to prevent essential fatty acid deficiency [3]. Early lipid administration is also crucial for minimizing the risk of hyperglycemia resulting from high glucose intake.

Indications of PN with all three macronutrients (dextrose + amino acids + lipids)

PN solutions that incorporate all three macronutrients are widely utilized in clinical practice. The addition of lipid emulsion provides additional calories, reduces the osmolarity of the solution, and prevents essential fatty acid deficiency. PN solutions containing all three macronutrients are commonly recommended for patients:

- Those in need of PN support for prolonged period.
- Patients requiring peripheral parenteral nutrition (PPN) with significant calorie supplementation but unable to tolerate carbohydrates.
- Critically ill patients, and those with hyperglycemia, diabetes mellitus, and respiratory failure.

DELIVERING PARENTERAL NUTRITION

For proper supplementation of PN, it is essential to understand different fundamental aspects of delivering PN, as classified below:

- Routes of nutrient delivery:

  Peripheral parenteral nutrition vs. central parenteral nutrition.
- Systems of delivering PN:

  Multiple bottle system, multi-chamber-bag PN, or hospital compounded PN.
- Duration of delivering PN:

  Continuous infusion of PN vs. cyclic infusion of PN.

Table 57.1 Comparison of peripheral and central parenteral nutrition

	PPN	CPN
Route of administration	Peripheral veins	Central venous access
Access site	Peripheral veins	Large peripheral veins or central veins
Location of catheter distal tips	Below the level of the axillary vein	Central circulation (usually SVC or uncommonly IVC)
Duration of therapy	less than 2 weeks	>7–14 days
Nutritional needs	Low	High
Daily caloric requirement	1000–1500	2000–3000
Daily volume need (mL)	2000–3000	1000–2000
PN osmolarity (mOsm/L)	Low (600–850)	High (>800–900)
Carbohydrate	30%	55%–60%
Fat emulsion	Major caloric source	Minor caloric source
Prerequisite	Good peripheral veins	Successful cannulation of large peripheral or central veins
Fluid permitted	No fluid restriction	Needs fluid restriction
Advantages	Easy insertion, lower risk of infection/complications	No limit to osmolality, pH, or volume of infusion
Disadvantages	Short life span, only for low osmolality infusion	Complex insertion, higher complication risk, and cost
Common complication	Thrombophlebitis of veins	Catheter sepsis

PICC: Peripherally inserted central catheter; CVCs: Central venous catheters; SVC: Superior vena cava; IVC: Inferior vena cava

A. Routes of nutrient delivery

The two routes used for nutrient delivery are peripheral parenteral nutrition, and central parenteral nutrition (CPN), which is compared in Table 57.1.

1. Peripheral parenteral nutrition

Peripheral parenteral nutrition is the frequently used method to deliver all the required nutrients through peripheral veins [4–6]. PPN aims to provide enough calories and nutrition for a short period (less than 2 weeks). PPN is generally intended when central PN is undesirable or unavailable.

Composition

The osmolarity of formulas for PPN should be less than 900 mOsm/L [7]. Formulas for PPN contain low concentrated dextrose (5–10%) and amino acids along with concentrated, calorie-dense lipids (usually 20% lipid emulsion), which can provide the patient's average basal energy and protein needs [8]. Lipid emulsion is an essential part of PPN. Lipid emulsion reduces the osmolarity of PPN because of its low osmolarity (260 mOsm/L) and therefore decreases the risk of thrombophlebitis of peripheral veins.

Prerequisite

For PPN, the peripheral vein should be readily accessible, and fluid restriction should not be an issue.

Indications [9]

- Requirements of PN for a short period

(less than a week). Postoperative patients requiring PN support are the most suitable candidates for PPN.

- Nutritional needs <1500–1800 kcals per day.
- Central venous catheter insertion is not possible, carries a high risk, or is contraindicated (e.g., patients with coagulopathy).
- Sepsis or bacteremia in patients with CPN to avoid central vein catheterization for a few days.

Contraindications

- In patients with high nutritional requirements (i.e., hypermetabolism, preexisting moderate to severe malnutrition, or high risk of protein depletion), PPN is not suitable, as it cannot provide enough nutrients.
- Patients who need fluid restriction (oliguric patients and edematous patients due to cardiac, hepatic, or renal failure).
- Critically ill patients who will not tolerate the high fluid volume of PPN required for providing their increased nutritional needs.
- If PPN does not allow complete nutritional requirements, PN should be administered centrally.
- If PN is required for a prolonged period (>2 weeks).

Advantages

- Easy and safe venous access.
- It avoids morbidity and risks of CPN and saves the cost of a central catheter.

Disadvantages

- Larger volume is required to provide even maintenance nutritional requirements.
- Difficulty in meeting high nutritional requirements (because the volume required to provide the same is prohibitively high in sick patients).
- The concentration of nutrients in peripheral parenteral nutrition is kept low to prevent thrombophlebitis of peripheral veins. So, a larger volume is required to meet the nutritional needs compared to central parenteral nutrition formulas.

Prevention of thrombophlebitis due to PPN

Various measures, which can prevent or reduce thrombophlebitis, are:

- Add heparin (1U/ml of total volume) and low-dose hydrocortisone to the PPN formulas [10, 11].
- Place a glycerine trinitrate transdermal patch on the skin overlying the tip of the IV catheter.
- Topical NSAID creams and gel may inhibit the local inflammatory response.
- Limiting the osmolarity of PPN to 600 mOsm/L.
- Chang peripheral lines every 72–96 hours.

2. Central parenteral nutrition

Central parenteral nutrition is the most effective method to deliver high concentration PN in a smaller volume into large diameter central veins (usually superior vena cava or uncommonly inferior vena cava) in patients who needs PN for >7–14 days. It is important to remember that the location of the distal tip determines central versus peripheral venous access and not the site of catheter insertion. When the distal end is located in the large-diameter central vein, administered hypertonic and acidic PN solutions mix quickly with surrounding turbulent blood flow and therefore avoid complications due to the local irritation of veins such as thrombophlebitis.

Goals and indications

The goal of CPN is to provide nutritional maintenance requirements and correct existing nutritional deficits. CPN is mandatory to provide long term PN support (weeks, months, or years) when volume and concentration of solution preclude peripheral administration (i.e., osmolarity exceeds 800–900 mOsm/L, pH <5 or pH >9, or fluid restriction is necessary), and to provide greater nutritional requirements to moderately to severely stressed patients [12].

Composition

As per patients' requirements, the composition of solutions for CPN varies. Most of the CPN solutions contain a higher concentration of dextrose (50–70%) and amino acids (8.5–10%), which makes these solutions hypertonic (osmolarity of CPN 1000–1900 mOsm/L as compared to plasma osmolarity 280 mOsm/L). These hypertonic CPN solutions are too irritant for a peripheral vein and should be infused only through central venous access. For safe and adequate delivery of CPN, it is essential to establish central vascular access with proper selection of the type of catheter and the site of insertion.

CPN permits the administration of a lower amount of fat emulsion than PPN because a higher concentration of dextrose and amino acids in CPN provides a significant amount of calories.

Selection of catheter for CPN

For CPN, a catheter made up of polyurethane and silicone is used routinely. Catheters made up of polyurethane are selected for short-term and medium-term use [12]. The advantage of polyurethane catheters is decreased catheter breakage but has a greater risk of thrombosis and catheter-related infection [13–15]. Silicon rubber catheter is preferred for long term or life-long PN therapy because of the reduced risk of thrombosis and infection, and is appropriate for using ethanol locks (to prevent bloodstream infections), but has decreased mechanical stability [14, 16]. Antimicrobial impregnated central venous catheters are superior in reducing central venous catheter-related bloodstream infection (CRBSI) [17].

Sites for insertion of a catheter for CPN

Short-term central access: Central venous access through a percutaneous non-tunneled catheter is commonly used and preferred for patients in the acute care setting for short duration therapies (<14 days) [12, 18]. In this method, the catheter is placed via the Seldinger technique into the internal jugular, subclavian, or femoral veins. For CPN, an upper body insertion site is preferred, and femoral vein catheterization is discouraged because of the higher risk of infection and thrombotic complications [19, 20].

This approach has the advantage of easy insertion, lesser cost, and better patient comfort and mobility for the short-term need. However, when the patient needs central venous access for the long-term PN, avoid this modality due to a higher risk of infection.

Percutaneous inserted central catheter (PICC): A 50–60 cm long polyurethane catheter is inserted in a peripheral vein in the antecubital area of the arm (cephalic or basilic vein) and threaded into the subclavian vein in such a way that the catheter tip is placed in the lower portion of superior vena cava or right atrium.

The use of PICCs is preferred in adult patients for short-term and medium-term PN (usually more than 2 weeks or less than six months) [21–24].

The use of PICCs has grown substantially in recent years because they are convenient, carry a low risk of placement-related complications, and are long-lasting and cost-effective.

The use of PICCs has grown substantially in recent years because it is convenient, low risk of placement-related complications, long-lasting and cost-effective [18, 25]. However, PICCs are associated with a higher risk of catheter-related venous thrombosis [18, 24, 26–28]. The PICCs are also associated with a higher risk of catheter-related bloodstream infection [18, 22, 29, 30], but the supporting evidence is insufficient [24, 25, 31–33].

While using PICC, to reduce the risk of infection, use the sutureless device and secure the catheter (to prevent migration of catheter) by subcutaneously anchored stabilization device [24, 34].

Long-term central access: "Tunneled" catheters (such as Hickman, Broviac, Hohn, or Groshong) and implanted subcutaneous ports are more stable, acceptable, and safe for patients who need PN for medium or long-term use (e.g., >3 months-years) [12]. The tunneled device is preferred in patients who require daily or routine access for long term PN [23, 35]. Implanted ports are cosmetically more desirable, have lower rates of infection [36], and are preferred when the need for access is less frequent (e.g., medication like chemotherapy) but rarely used for PN due to the requirement of venous access regularly [35].

"Tunneled" catheters are usually placed in the subclavian or internal jugular vein, with the distal tip positioned in the lower portion of the superior vena cava. After exiting from great veins, the "Tunneled" catheter traverses for about 10 cm under the skin in the subcutaneous tunnel, with the external portion of the catheter lying on the anterior chest wall.

The femoral vein is not preferred and usually avoided for long-term central access for PN due to the high risk of infection at the exit site (at the groin) and an increased risk of venous thrombosis [12]. A subcutaneous tunnel is created, so the catheter exits from the skin several inches away from the venipuncture location.

The tunnel acts as a barrier and reduces the risk of infection substantially. The dacron cuff around the catheter is positioned in the subcutaneous tissue 2 to 3 centimeters from the exit site, stabilizing the catheter and acting as a mechanical barrier limiting bacterial entry and preventing ascending microbial infection [16].

Methods used to confirm the catheter tip position are chest radiography, fluoroscopy, point-of-care transthoracic echocardiography, or continuous electrocardiography [19, 37, 38]. In addition to accurately assessing the position of the tip of the catheter, a post-procedure chest X-ray also detects pneumothorax, malpositions, and kinking [39].

The central line must be handled with a strict aseptic technique for safe use, and the single-lumen catheter is preferred to prevent infection. Use a central line exclusively for administering PN and avoid its usage for administering of IV solutions or medications, blood sampling, and central venous pressure (CVP) monitoring.

B. Systems of delivering parenteral nutrition

Three different systems used for delivering parenteral nutrition are a "multiple bottle" system, commercially available multichamber bags parenteral nutrition (MCB-PN), and hospital compounded parenteral nutrition.

1. Multiple bottle system

In the past, separate bottles were used to infuse individual substrates (carbohydrates, lipids, and amino acids) for PN [40, 41]. The advantages of multiple bottle systems are lower cost, flexibility, and ease of making adjustments in PN composition, particularly in critically ill patients with rapidly changing requirements [42].

Disadvantages of multiple bottle system are [40, 42]:

- Frequent manipulations during administering PN through multiple bottle systems carry a greater risk of nosocomial infections.
- Adjustment of different flow rates for different nutrients, adding different minerals and vitamins, and monitoring hyperglycemia, hypertriglyceridemia, and electrolyte disorders in each patient are cumbersome and are not without frequent mistakes.
- Simultaneous administration of various nutrients without maintaining proper proportion carries the risk of physicochemical incompatibilities.
- When costs of disposables and time spent by the nurse for administration of PN are considered, a multiple bottle system is costlier than commercially available multichambered PN formulations [43].

2. Multichamber-bag PN (MCBPN)

These products are standardized, easy-to-use nutrient mixtures, commercially available as two or three-chamber bags. Two-chamber bag systems ("2CB" or 2 in 1 formulation) contain dextrose and amino acids with or without electrolytes. Three-chamber bag systems (all-in-one admixture (AIO), "Three in One" system, 3 in 1 formulation) contain dextrose, amino acids, and lipid injectable emulsion (ILE), with/without electrolytes.

The advantages of three multichamber-bag PN products are:

- Convenience: The easy, convenient, and most preferred way for the single-line administration of PN. As all nutrients are available in a single container (referred to as premixed, "ready-to-use" commercial bags), it saves time and reduces the workload [44, 45].
- Less infection: Decrease bloodstream infection rates due to less handling during preparation and delivery (reduced connections and reduced need of changing bags) [46–49].
- Safer: Lesser chances of various calculations and compounding human errors and better stability and sterility as manufactured with high standards [44, 45, 50].
- Recommended standard practice: SCCM-ASPEN guidelines (2016) and other literature recommend using standardized commercially available PN formulations compared to compounded PN admixtures when the formulation meets the patient's metabolic needs [1, 51, 52].
- Lower cost: Cost-saving during preparation, handling, and delivery (requiring fewer bags and tubings and no extra pump for lipid emulsion) [40, 49, 53–55].
- Due to slow continuous infusion, better assimilation, and utilization of nutrients with lesser chances of metabolic complications.
- Storage is more convenient with long shelf life [44].

Disadvantages of Multichamber-bag PN are:

- Lack of flexibility: Changes in composition/proportion of contents are not possible.
- Inappropriate overuse due to easy commercial availability of different formulations with a wide choice.
- Absence of transparent color: Due to the presence of lipids, three in one

solution is opaque, which impairs visual inspection of the solution for particulate matter, precipitation, or fungal growth.

3. Hospital compounded PN admixture

This PN formulation containing various nutrients is designed to meet the nutritional needs of specific clinical conditions. Aseptic tailormade compounding of PN admixture in a hospital needs a sophisticated manufacturing system and skilled pharmacists, so its availability is problematic. The use of personalized hospital compounded PN is decreasing because of multiple limitations [56–59] and a greater risk of sepsis [60].

C. Duration and mode of delivering parenteral nutrition

Two methods used for administering PN include continuous infusion of PN and cyclic infusion of PN.

1. Continuous parenteral nutrition

Parenteral nutrition infuses over 24 hours continuously at a constant rate by a pump. Continuous PN is the most common regimen used for acute, critical, and hospitalized patients. Slow continuous infusion of PN by infusion pumps avoids volume overload and side effects secondary to rapid administration of carbohydrates and lipids (such as hyperglycemic and triglyceridemia), allows better utilization of nutrients, and provides nutritional requirements throughout the day. Drawbacks of this modality are poor mobility due to attachment to the pump and increased risk of fatty liver due to continuous high insulin levels.

2. Cyclic/intermittent parenteral nutrition

Cyclic/intermittent PN is the method in which PN is infused at a higher rate over 10 to 14 hours (typically at night when the patient is sleeping) and then stopped [61]. Cyclic PN improves the quality of life, decreases the incidence of hepatobiliary complications, and may limit or reverse PN-associated liver dysfunction [62–64]. In addition, this regimen allows for a 10 to 14 hour break each day from the pump, enabling the person to engage in normal daily activities. Cyclic PN should be attempted cautiously in the presence of glucose intolerance, edema, or fluid tolerance and is not suitable for critically ill patients [52]. However, cyclic PN is effective and safe for stable, chronically ill patients who require long-term nutrient support (e.g., home parenteral nutrition) [65].

DESIGNING PARENTERAL NUTRITION FORMULA

PN is a high-alert medication, and planning appropriate and safe prescriptions for the individual is complex. The parenteral nutrition formula can be designed by following steps:

Step 1: Calculate the daily nutritional requirements and convert them into a prescription.

Step 2: Choosing the appropriate commercially available formula for the infusion.

Step 1: Calculate the daily nutritional requirements and convert them into a prescription

The first step in preparing a PN prescription is to calculate the daily nutritional requirements. It is essential to conduct a comprehensive evaluation of the patient and take into account all the factors that influence these requirements (refer to Table 57.2) to determine these requirements.

Sample calculation of the daily requirements of energy, protein dextrose, and lipids with consideration of fluid for a 60 kg patient, who is stable, euvolemic with good urine output and moderate stress is summarized below:

- Fluid requirement: Approximately 35 mL/kg.

  So, 35 (mL/kg) × 60 (kg) =
  2100 ml/day.
- Caloric requirements: Approximately 25 kcal/kg.

  So, 25 (kcal/kg) × 60 (kg) =
  1500 kcal/day.
- Protein requirements: For stable patients, 1 gm/kg body weight.

  So, 1 (gm/kg) × 60 (kg) =
  60 gm/day.

  1 gm of protein provides 4 kcal, so 60 gm of protein will provide 60 × 4 = 240 kcal.
- Lipids requirements: 30% of total calories.

  So, 30% of 1500 (kcal/day) =
  450 kcal.

  1 gm of fat provides 9 kcal, so to provide 450 kcal, 450/9 = 50 gm of fat will be required.
- Carbohydrate requirement:

  Total caloric requirements minus the sum of protein and fat calories.

  So, 1500 – (240 + 450 kcal) =
  1500 – 690 = 810 kcal.

  1 gm of dextrose in solution provides 3.4 kcal. So to provide 810 kcal, 810/3.4 = 238 gm of dextrose will be required.

So, the total daily requirement of the patient is 2100 ml fluid volume, a total calorie requirement of 1500 kcal, 60 gm of amino acids, 50 gm of fat, and 238 gm of dextrose. In addition, electrolytes, trace elements, and vitamins should be added as per requirement.

Step 2: Choosing the appropriate commercially available formula for the infusion

According to the prescription, the PN solution is prepared either in a hospital pharmacy or a commercially available formula that best matches the prescribed nutrients is chosen for administration. Micronutrients are coadministered in the proper dose.

PN solution is prepared in hospital pharmacies only for a limited number of patients due to lack of facilities, higher risk of sepsis, and no advantage in clinical outcomes [1]. Due to these limitations, standardized commercially available PN products are widely used and preferred over tailormade hospital compounded PN solutions.

One or more commercially available readymade PN solutions that closely

Table 57.2 Factors determining PN requirements
• Weight of the patient
• Clinical status: stable or critical
• Medical or surgical conditions for which PN is indicated
• Nutritional status/malnutrition, volume status, urine volume
• Coexisting disorders (diabetes, hypertension, congestive heart failure, renal disorders, liver diseases, pulmonary diseases, sepsis, etc.)
• Electrolyte and acid base status

match the prescription are selected.

The volume of fluid permitted to the patient and the concentration of nutrients in the PN solution are inversely proportionate. Select a PN solution with a greater concentration of various nutrients if the patient needs fluid restriction (e.g., central PN). When the patient needs PN, and a larger fluid volume is permitted, a PN solution with a low concentration of nutrients (e.g., in peripheral PN) is selected.

Various commercially available PN products and their classification based on their composition and routes of administration (peripheral vs. central venous access) are summarized in Table 57.3 and Table 57.4. In addition, the classification of various lipid emulsion products based on their lipid source is summarized in Table 57.5. A summary of commercially available PN products in these tables can assist clinicians in selecting PN solutions quickly and accurately.

Table 57.3 Commercially available products for peripheral PN and their composition

Solution	Manufacturer	Volume (ml)	Calorie (kcal)	Osmolarity mOsm/L	Dextrose (gm)	Amino acids (gm)	Lipids (gm)
Amino acid containing solutions							
Aminosyn-PF 7%	Hospira	500	140	561	-	35	-
Aminoven 5%	Fresenius Kabi	500	100	490	-	25	0
Aminoven infant 10%	Fresenius Kabi	100	4	885	-	10	0
Amino acid and dextrose containing double chamber bag							
Aminomix peripheral	Fresenius Kabi	1000	390	770	63	35	-
Aminosyn II 4.25%/10%	Pfizer/Hospira	1000	483	894	100	42.5	-
Clinimix 4.25/10	Baxter	1000	510	930	100	42.5	-
Nutriflex peri	B Braun	1000	480	900	80	40	-
Lipid emulsions							
Intralipid 10%	Fresenius Kabi	500	550	260	-	-	50
Intralipid 20%	Fresenius Kabi	500	1000	260	-	-	100
Lipofundin MCT/ LCT 20%	B Braun	500	954	380	-	-	100
Clinolipid 20%	Baxter	500	1000	270	-	-	100
Lipoplus	B. Braun	500	955	410	-	-	100
SMOFlipid 20%	Fresenius Kabi	500	1000	270	-	-	100
Amino acid, dextrose and lipid containing triple chamber bag							
Kabiven peri	Fresenius Kabi	1440	1000	750	97	34	51
Nutriflex lipid peri	B Braun	1000	765	840	64	32	40
PeriOlimel N4	Baxter	1000	700	760	75	25.3	30
Smofkabivan peri	Fresenius Kabi	1448	1000	850	103	46	41

Table 57.4 Commercially available products for Central PN and their composition

Solution	Manufacturer	Volume (ml)	Calorie (kcal)	Osmolarity mOsm/L	Dextrose (gm)	Amino acids (gm)	Lipids (gm)
Amino acid containing solutions							
Aminoven 10%	Fresenius Kabi	1000	400	999	-	100	-
Aminosyn 10%	Hospira	1000	400	938	-	100	-
FreAmine 10%	B Braun	1000	388	950	-	97	-
Travasol 10%	Baxter	1000	400	999	-	100	-
Amino acid and dextrose containing double chamber bag							
Aminomix Novum	Fresenius Kabi	1000	1000	1779	200	50	-
Aminosyn II 4.25%/20%	Pfizer	1000	850	1295	200	42.5	-
Clinimix 8/10	Baxter	1000	663	1308	100	80	-
Nutriflex plus	B Braun	1000	792	1400	150	48	-
Amino acid, dextrose and lipid containing triple chamber bag							
Kabiven	Fresenius Kabi	1026	872	1060	100	34	40
Nutriflex lipid plus	B Braun	1250	1265	1540	150	48	50
Olimel N9/ Triomel N9	Baxter	1000	1070	1170	110	56.9	40
Smofkabivan	Fresenius Kabi	986	1100	1500	125	50	38

Table 57.5 Commercially available lipid emulsion products and their composition

Lipid source	Product	Manufacturer	Soybean oil	MCT oil	Olive oil	Fish oil	ω-6: ω-3 Ratio
Soybean oil-based	Intralipid Ivelip Lipofundin N Liposyn III	Fresenius Kabi Baxter B Braun Hospira	100%	-	-	-	7:1
SO/MCT-based	Lipofundin MCT/LCT	B Braun	50%	50%	-	-	7:1
	Structolipid	Fresenius Kabi	64%	36%	-	-	7:1
Olive oil-based	ClinOleic Clinolipid	Baxter Baxter	20%	-	80%	-	9:1
Fish oil containing emulsions	Lipoplus (Lipidem)	B Braun	40%	50%	-	10%	3:1
	SMOFlipid	Fresenius Kabi	30%	30%	25%	15%	2.5:1
	Omegaven	Fresenius Kabi	-	-	-	100%	1:8

INITIATION OF PN

- It is essential to evaluate the patient's nutritional status by careful history, physical examination, and laboratory studies before initiation of PN.
- PN may be initiated in hemodynamically stable patients who can tolerate the fluid volume. Correct electrolyte abnormalities and hyperglycemia before the initiation of PN.
- PN should be initiated slowly (no more than 50% of the calculated requirements on the first day) to avoid adverse effects like hyperglycemia and electrolyte disturbances [66]. PN is increased gradually over 4 to 7 days to achieve the nutrition goal.
- PN may precipitate refeeding syndrome in severely malnourished patients due to rapid fall in potassium, magnesium, and phosphorus levels. So slow initiation and close monitoring of the patient's electrolytes is necessary to avoid adverse effects on cardiac and respiratory function.

Care of PN mixture

- Store reconstituted PN bags in a refrigerator until 30 min before using.
- Always examine the PN solution before administration to exclude particulate matter, cloudiness, or an oily layer in the bag.
- Follow strict aseptic techniques while connecting and administering PN.
- To administer dextrose/amino acids PN formulations, use an infusion set with an in-built air vent and a 0.22-micron filter [52]. For administering lipids containing PN formulations, use a 1.2 micron - larger sized filter to avoid clogging of the filter.
- Do not use a three-way stopcock as it increases the risk of infection.
- Do not insert a needle for air venting in a PN bag.
- Do not add any medication to the PN bag.
- Do not allow the PN solution to hang for more than 24 hours.
- Do not use the PN line to draw blood for the test, administer medications, or measure central venous pressure.

MONITORING OF PN

Every patient receiving PN should be monitored carefully for the prevention or early detection of complications and to judge the effectiveness of therapy. Meticulous monitoring is aimed at monitoring, detecting, or assess:

- Metabolic status, including hyperglycemia and hypoglycemia.
- Risk of refeeding syndrome or clues of overfeeding.
- Micronutrient deficiency and toxicity.
- Fluid and electrolytes status.
- Catheter-related complications, including sepsis.
- Hepatic and other long-term complications.

A clinical data and laboratory study used routinely for monitoring patients receiving PN is summarized in Table 57.6:

- Always obtain a chest X-ray to check catheter placement after insertion.
- Record vital signs at least every 4 hours. Temperature elevation is one of the earliest signs of catheter-related sepsis.
- Patients should be weighed daily at the same time each morning after voiding on the same scale. Weight gain may indicate fluid overload.
- Perform site care and dressing change at least three times weekly or whenever the dressing becomes wet.

Table 57.6 Monitoring the patient on parenteral nutrition

Clinical data monitoring
History: Focused on patient's sense of well-being, strength to perform routine activities, fever, and medical history for signs of fluid overload or glucose and electrolyte imbalance. **Vital signs:** Monitor temperature, pulse, blood pressure, and respiratory rate. **Fluid balance:** Strict input/output chart, daily weight, and signs of fluid overload or dehydration. **Local care:** Inspecting and dressing vascular access site (to rule out infection). **Delivery system:** Inspection of solution for contamination and watch for the proper functioning of infusion pump, catheter function, and timely changing of tubing and bags.

Monitoring of laboratory data during PN			
Parameter	**Baseline and initial period**	**Stable period**	**Long term**
Blood glucose	6 hourly	1–2 times/ week	Monthly
BUN, creatinine, electrolytes, HCO_3, PO_4, Ca^{2+}, Mg^{2+}	Daily	Weekly	Monthly
CBC, liver function test (LFT), triglycerides, PT	Weekly	Weekly	Monthly
Micronutrient tests, as indicated			

- Patients receiving PN should be monitored carefully to detect early signs of complications such as fluid overload, electrolyte imbalances, nutritional problems, or allergic reactions.
- Monitor serum glucose levels every 6 hours initially, then once a day. Watch for the symptoms of hyperglycemia, such as thirst and polyuria. Maintain blood glucose <180 mg/dL [1, 67].
- Monitor renal function, electrolyte levels, liver function, phosphate, calcium, and magnesium daily in the first week of initiating PN. Once the patient is stable, these tests are performed once or twice a week and less frequently in the long term.
- Monitoring response to nutritional therapy. There is no single criterion that can reliably indicate the effectiveness of PN. Improvement in clinical status and visceral protein concentrations (e.g., albumin, prealbumin, and transferrin) are most commonly used to monitor nutritional status. When interpreting visceral protein values, it is essential always to consider the patient's fluid status, organ function, and presence of infection. If nutritional recovery is inappropriate, a nitrogen balance study may guide changes in amino acid intake. Similarly, if traditional methods of calculating calorie requirements are unsatisfactory, indirect calorimetry is indicated.
- If the patient receiving PN develops fever, chills, or hypotension, its most common cause is a catheter-related bloodstream infection. Therefore, for diagnosis of CRBSI, blood cultures should be drawn immediately before initiating antibiotic therapy.

TERMINATION OF PN

- PN is the temporary method of nutritional supplementation. The ultimate goal is slow and smooth transit from PN to oral/enteral food intake once the gastrointestinal function returns.
- During the transition period, discontinue PN when the patient can tolerate

60–70% of the total nutritional requirements orally or enterally.

- If the patient cannot tolerate oral or enteral supplementation and intake is less than 60% of nutritional requirements, restart PN in 2–3 days.
- Plan a gradual transition from PN to oral or enteral nutrition to avoid overfeeding during the phase of reduction of PN and worsening of nutritional status when PN is discontinued.
- If there is a need for abrupt discontinuation of PN, administer 10% dextrose for a few hours to prevent hypoglycemia.
- After discontinuing PN, monitor blood glucose closely for several hours to detect hypoglycemia.
- During the transition period, closely and carefully monitor clinical status, hydration status, weight, and laboratory tests.

COMPLICATIONS OF PARENTERAL NUTRITION

The primary complications of parenteral nutrition include mechanical, metabolic, and infectious complications. However, most complications are reduced with careful management and supervision by an experienced nutritional support team. Commonly encountered complications are summarized in Table 57.7.

MECHANICAL COMPLICATIONS

Potential mechanical complications related to central venous catheter placement are malposition of the catheter, pneumothorax, hemothorax, arterial injury, thoracic duct injury, nerve injury, air embolism, cardiac arrhythmia, and cardiac perforation with tamponade.

Table 57.7 Complications of PN

	Mechanical	Metabolic/GI	Infectious
First 48 hours	Malposition, Haemothorax Pneumothorax Chylothorax Air embolism, Cardiac arrhythmia Injury to the subclavian/carotid artery	Fluid overload Hyperglycemia Hypophosphatemia Hypokalemia Hypomagnesemia Refeeding syndrome	-
First two weeks	Catheter displacement Catheter thrombosis Catheter occlusion Air embolism	Hyperglycemic coma Acid base imbalance Electrolyte imbalance	Catheter induced sepsis Exit site infection
Three months induced onwards infection	Fracture or tear of the catheter Catheter thrombosis Air embolism Blood loss	Essential fatty Acid deficiency Vitamin or trace element Deficiency PN metabolic Bone diseases PN liver diseases	Tunnel infection Catheter Sepsis Exit site

Ultrasound-guided central venous catheter insertion by trained and experienced personnel can reduce mechanical complications significantly [68].

Post subclavian and jugular CVC insertion, chest X-ray in the upright or semi-upright position is helpful to exclude malposition of the catheter, pneumothorax, or hemothorax and confirm the correct tip position (in the inferior third of superior vena cava or at the junction of the superior vena cava and the right atrium, parallel to the vessel wall). Avoid excessive advancement of a catheter because the tip of the CVC in the cardiac chamber carries the risk of cardiac arrhythmia. It is also important to avoid the inadequate length of insertion because the infusion of high osmolarity PN solutions with a catheter tip at a higher level can cause direct damage to the vein (thrombophlebitis) [69].

The osmolarity of PN solutions is three to eight times the normal serum osmolality. PN with high osmolarity in the long term can cause injury to endothelium and vein wall inflammation with resultant upper extremity deep venous thrombosis.

Most patients are asymptomatic, but swelling of the neck or arm with erythema, tenderness, and warmth is the common presentation in a few patients [70].

Catheter-related thrombosis is treated primarily with anticoagulation, and thrombolytic therapy is offered in selected patients having a high risk of thrombosis [71]. Removal of the catheter is recommended in catheter-related thrombosis if the catheter is non-functional or not needed, anticoagulation is contraindicated, inadequate improvement in symptoms with anticoagulation, or the thrombosis is limb or life-threatening [70, 71].

CATHETER-RELATED BLOODSTREAM INFECTION

In patients receiving CPN, catheter-related bloodstream infection (CRBSI) is the most common and serious complication that increases hospital stay and cost and is associated with significantly high morbidity and mortality.

In most cases, it is preventable with proper aseptic techniques and is often related to non-adherence to aseptic techniques, suboptimal catheter care, and inadequate patient education.

The upper body insertion site (internal jugular or subclavian vein) is preferred over the femoral site to reduce the risk of infection [19].

CRBSI is usually caused by the migration of skin organisms at the catheter exit site for short-term catheters and direct contamination of the catheter or catheter hub in long-term CVC [72].

The risk of line infection can be minimized by:

- Strict asepsis when handling (connecting/disconnecting) the line.
- Single-lumen central venous catheters should be dedicated solely to the infusion of parenteral nutrition.
- Use of a dedicated lumen on a multiple lumen CVC or a PICC line for administration of PN.
- Use of antibiotic-coated or antibiotic-impregnated catheters.

Fever in a patient with no other identifiable infection source raises suspicion of catheter-related infection. Staphylococcus and candida are the most frequent pathogens. Whenever catheter-related sepsis is suspected, the following steps should be considered:

- Evaluate the catheter insertion site and culture any drainage.

- Obtain blood cultures: For diagnosis of CRBSI, blood cultures should be drawn from each lumen of the catheter and two sets of blood cultures from peripheral veins via separate venipuncture sites before initiating antibiotic therapy [73]. Catheter tip cultures cannot be used as a substitute for blood cultures to confirm catheter-related bloodstream infection [74, 75].
- Begin empiric antibiotic therapy:

  In uncomplicated patients, it is unnecessary to remove the CVC. Instead, treat CRBSI immediately by administering broad-spectrum antibiotics through the lumen to salvage the catheter.

  It is unnecessary to remove the CVC in uncomplicated patients and treat CRBSI immediately by administering broad-spectrum antibiotics through lumen for catheter salvage.
- Remove catheter: Indications of catheter removal are [76]:
  - Tunnel and pocket infections.
  - Clinical deterioration, septic shock, or presence of severe complications such as endocarditis, septic thrombosis, or abscess formations.
  - Repeated positive blood culture besides antibiotic therapy.
  - Although guidewire exchange has a lower risk of technical complications, it is not recommended as an alternative approach to removal.

METABOLIC COMPLICATIONS

The most common problems caused by PN are hyperglycemia, fluid overload, electrolyte imbalances, refeeding syndrome, and hepatobiliary complications. Therefore, proper monitoring and adjustments in the composition and rate of PN are essential to reduce the metabolic complications caused by PN.

A. Hyperglycemia

Hyperglycemia occurs in more than half of patients receiving PN [77, 78] and is associated with increased hospital complications and mortality [77, 79].

The risk factors for hyperglycemia are excess and rapid administration of dextrose, obesity (BMI>25 kg/m2), preexisting diabetes mellitus or liver impairment, hyperglycemia before starting PN, surgical indications of PN, corticosteroid use, presence of infection, and critical illness [78, 80, 81]. Hyperglycemia in a previously normoglycemic patient should also raise suspicion of infection.

Hyperglycemia is the greatest danger from PN during the first 24 hours. It may lead to osmotic diuresis and glycosuria, leading to excessive excretion of free water by the kidney, thus causing hyperosmolar nonketotic dehydration, coma, and even death. Therefore, it is best treated by prevention.

As blood glucose values above 180 mg/dL are associated with a higher incidence of complications [77], the current recommendation is to keep glucose concentration 140–180 mg/dL [82–85].

Various insulin regimens used to control hyperglycemia in patients receiving PN are [86]:

- **Continuous intravenous insulin infusion:** Ideal for unstable and critically ill patients receiving PN requiring maximal flexibility in dose modifications.
- **Insulin added to PN:** Directly adding insulin to the parenteral nutrition bag is a convenient and physiologically favorable method to treat

hyperglycemia, particularly in general wards where separate IV insulin administration may not be feasible. However, this method is inappropriate in unstable patients and increases the risk of infectious complications.

- **Insulin added to PN and supplemental subcutaneous insulin using a sliding scale:** This regimen is widely used for non-critically ill T2DM patients and provides better glycemic control after PN interruption [87].
- **Subcutaneous insulin injection:** This regimen is useful in stable patients on PN before discontinuation of IV insulin for transitioning from IV to subcutaneous insulin administration.

Measures to prevent hyperglycemia during PN administration

- Do not overfeed the patient (starting dose less than 20–25 kcal/kg/d).
- Restrict dextrose in PN to 100–150 gm/day initially and administer it slowly (2–3 mg/kg/minute).
- Increase the portion of lipid administration if needed (to supply calories and to limit the required dextrose).
- Consider other sources of IV dextrose such as peritoneal dialysis solution, antibiotic drips, etc.
- Monitor blood glucose closely (every 4–6 hours) and increase insulin doses accordingly.

B. Hypoglycemia

Although the incidence of hypoglycemia is low among hospitalized patients receiving PN, it needs careful attention because of its detrimental consequences [88, 89].

PN associated hypoglycemia may be a consequence of:

- Overtreatment of hyperglycemia with the use of insulin via PN, IV infusion, or subcutaneous injection. The risk of hypoglycemia is higher when insulin is administered by drip.
- "Rebound hypoglycemia" after abrupt discontinuation of PN formulations (e.g., cyclic infusion of parenteral nutrition) [65].

Patients prone to develop hypoglycemia are advanced age, poor nutritional status, previous history of diabetes, renal failure, liver disease, ICU patients, patients on long-term PN, insulin administered by drip, and inadequate monitoring [88].

Measures to prevent hypoglycemia are:

- Slow tapering: Before discontinuing of the PN, tapper down infusion at half the rate for 1–2 h to reduce the risk of rebound hypoglycemia.
- If PN infusion needs to be discontinued abruptly, administer dextrose-containing fluid for about 1 or 2 hours to avoid the risk of hypoglycemia.
- When insulin is added to the PN solution, the risk of hypoglycemia is low on abrupt discontinuation of PN.
- As aggressive treatment of hyperglycemia to achieve tight blood glucose control carries the risk of hypoglycemia, a target blood glucose in the range of 140–180 mg/dL is recommended to reduce the incidence of hypoglycemia [82].
- Close monitoring of blood glucose and meticulous adjustment of insulin dosage (avoid higher insulin to dextrose ratio in PN).

C. Refeeding syndrome

This is a potentially serious but often neglected condition that can occur due to shifts of fluid, electrolytes, metabolic, and vitamin disturbances during re-initiation of nutritional therapy in patients with malnutrition or prolonged fasting. It can cause significant morbidity and even mortality.

Common high-risk factors for refeeding syndrome are [90, 91]:

- Severe malnutrition, BMI less than 18.5 kg/m2, recent weight loss (>10% within the last 3–6 months), poor or no nutritional intake for more than 5 days.
- Alcoholism abuse, anorexia nervosa, depression, bariatric surgery, bowel resections, malabsorption, insulin, chemotherapy, antacids, or diuretics.
- Low baseline levels of phosphate, potassium, or magnesium.

Pathophysiology: Refeeding syndrome is related to the shift from the catabolic to the anabolic metabolic pathways, which occurs with the reintroduction of glucose (refeeding) after a prolonged phase of starvation [92].

During the starvation (catabolic) period, the body adapts to less carbohydrates; fat becomes the primary source of energy requirements, and levels of blood glucose and insulin decline.

Prolonged fasting leads to severe depletion of intracellular phosphate, potassium, and magnesium and deficiencies of various vitamins, including thiamine.

The initiation of carbohydrate-containing nutrition leads to a rise in blood glucose levels, which in turn causes a rapid increase in insulin secretion.

Endogenous insulin surge causes massive shifts of phosphorus, potassium, and magnesium intracellularly, leading to severe hypophosphatemia, hypokalemia, hypomagnesemia, and potentially lethal complications. Hypophosphatemia is the hallmark of the syndrome.

Thiamine requirements increase significantly during the nutritional replenishment, so in the state of thiamine deficiency, re-initiation of feeding can cause metabolic acidosis and neurologic abnormalities (i.e., confusion, Wernicke's encephalopathy or dry beriberi) or cardiovascular complications (i.e., peripheral edema, congestive heart failure, or wet beriberi). In addition, thiamine is an essential coenzyme in carbohydrate metabolism. Therefore, glucose is converted to lactate instead of adenosine triphosphate (ATP) via the Krebs cycle, causing lactic metabolic acidosis when thiamine is lacking.

Clinical features: Symptoms generally appear within the first 2–5 days of initiating nutritional therapy, and it's highly variable, ranging from mild to severe and life-threatening, depending on the severity of malnutrition and comorbidities [92]. The clinical symptoms of the refeeding syndrome are nonspecific and chiefly due to underlying hypophosphatemia, hypokalemia, hypomagnesemia, sodium retention, and thiamine deficiency:

- Cardiovascular: Fluid overload, congestive heart failure, arrhythmias, bradycardia/tachycardia, and hypotension.
- Respiratory: Respiratory failure, pulmonary edema, hypoventilation, and failure to wean from the ventilator.
- Neurological: Paraesthesia, ataxia, delirium, Wernicke's encephalopathy.
- Musculoskeletal: Weakness, fatigue, myalgias, and rhabdomyolysis.
- Miscellaneous: Abdominal pain, constipation, vomiting, anemia, metabolic acidosis.

Measures for the prevention and treatment [91–95]

- Search and recognize high-risk patients for refeeding syndrome.
- Order baseline laboratory tests to assess potassium, magnesium, and phosphorus status before initiating nutrition support.

- Prophylactic administration of adequate electrolytes (even if blood levels are in the low-normal range), vitamin (thiamine, water, and fat-soluble), and micronutrient (Zn, Fe, Se) in "standard" maintenance doses, concurrently with the nutrition support. An approximate daily dose of electrolytes supplementation suggested is 1–1.5 mEq/kg potassium, 0.2–0.4 mEq/kg magnesium, and 0.3–0.6 mmol/kg phosphate. If values of electrolytes are severely low, it is recommended to delay the initiation of nutrition support until the electrolyte imbalances are corrected.
- The recommended dose of thiamine is 100 mg per day, to be administered before initiating dextrose-containing IV fluids and to be given for a period of 5–7 days or longer.
- Start refeeding gradually and cautiously in a stepwise manner to avoid excessive nutritional replenishment and limit the resultant risk of refeeding syndrome. First, start caloric supplementation in low dose (no more than 50% of energy requirements [NICE guidelines] or 100–150 gm of dextrose or 10–20 kcal/kg for the first 24 hours [ASPEN guidelines 2020]) and increase the dose slowly (advance by 33% of a goal every 1 to 2 days).
- Careful administration of sodium and fluids to avoid fluid overload.
- Close clinical and laboratory indices monitoring. Measure vital signs every 4 hours on the first day and maintain daily weight and intake output chart. Monitor serum potassium, magnesium, and phosphorus every 12 hours for the first three days.
- If overt symptoms and abnormal electrolyte values, curtail nutritional supplementation. In patients with refeeding hypophosphatemia, reduce energy intake temporarily or restrict it for 48 hours and gradually increase subsequently. Reduce fluid intake if edema or congestive heart failure and replace electrolytes aggressively according to the serum electrolyte levels.

D. Hepatic abnormalities

In patients receiving parenteral nutrition, liver diseases are common, and their prevalence ranges from 4.3% to 65% [96, 97]. Three major and most frequently encountered hepatobiliary complications are steatosis (accumulation of fat in the liver due to overfeeding), cholestasis (impaired or blocked secretion of bile), and gallbladder sludge/stones (due to gallbladder inactivity and stasis) [98, 99]. The broad spectrum of hepatic manifestations of PN-associated liver disease ranges from a benign and temporary rise in liver function tests to steatosis to fibrosis and, eventually, progress to portal hypertension and end-stage liver failure in a few [100]. Elevated serum conjugated bilirubin >2 mg/dL is the primary marker of PN-associated liver disease, which generally occurs early in therapy (within 2 weeks of initiation of PN). Therefore, when a patient receiving PN develops hepatic complications, it is essential to exclude other causes of liver disease.

Three terms used to describe the spectrum of liver disorders in patients receiving PN are PNAC (Parenteral nutrition-associated cholestasis), PNALD (Parenteral nutrition-associated liver disease), and IFALD (Intestinal failure-associated liver disease) [101]. Parenteral nutrition-associated liver disease is the general term used to describe the different hepatic and serum abnormalities associated with liver injury in adult and pediatric patients receiving long-term PN [102]. As long-term administration of PN can cause cholestasis, the term Parenteral nutrition-associated cholestasis (PNAC) is frequently used in the pediatric literature [103].

The term "Intestinal failure-associated liver disease" (IFALD) is now preferred to "PNALD" or "PNAC" for describing liver disease associated with PN in both pediatric and adult patients, as it more accurately reflects the multifactorial nature of the problem and its relation to intestinal failure [104, 105]. However, both terms, PNALD and IFALD, are used interchangeably in clinical practice to describe hepatic dysfunction secondary to intestinal failure in patients who are on PN.

Major risk factors for the development of PNALD are [98, 99]:

- Excessive energy intake or overfeeding.
- Glucose overload or excessive carbohydrate administration.
- Excess administration of lipid >1 gm/kg/d.
- Administration of soybean oil-based lipid emulsion.
- Continuous infusion of PN.
- Lack of enteral stimulation.
- Carnitine and choline deficiency.

Interventions recommended to prevent or treat hepatic complications are:

- Avoiding excessive calorie administration: Avoid administration of >25 to 30 kcal/kg calories to reduce the risk of steatosis or fat deposition in the liver.
- Avoiding excessive carbohydrate administration: Avoid administration of >5 mg/kg/min/d carbohydrate to prevent PNALD/IFALD [96].
- Appropriate carbohydrates to lipids ratio: PN solution should contain about 70–85% carbohydrates and 15–30% lipids to provide nonprotein energy [106].
- Restrict the dose of soybean-based lipid emulsions (<1 gm/kg body weight/d) to treat children with PNALD [21, 107].
- Change the composition of lipid emulsions: Supplementation (partial or complete) of omega-3-fatty acids enriched fish oil to soybean-based lipid emulsions (with the reduced n6/n3 ratio) is recommended to prevent and treat PNALD [103, 108–110].
- Prefer cyclic PN instead of continuous PN: Cyclic PN (9 for 12 to 16 hours) allows time for the mobilization of fats during the non-administration period of PN [105]. Therefore, a switch to cyclic PN infusion helps stabilize or improve impaired liver function [64, 65, 111].
- Early oral or enteral nutrition: Even small amounts of oral or enteral nutrition (EN) stimulates enterohepatic circulation of bile acids and reduce the risk for PNALD.

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